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International Journal of Biomedical Research Science

Vol. - 01 Number (1) Jan-Feb-Mar-Apr 2025

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1. Lindley, S. T., Estimation of population growth and extinction parameters from noisy data. Ecol. Appl., 2003, 13, 806-813.
2. Martin, H., The Archaean grey gnesisses and the genesis of continental crust. In Archaean Crustal Evolution (ed. Condie, K. C.), Elsevier, Amsterdam, 1994, pp. 205-259.

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International Journal of Biomedical Research Science (IJBRS)
An Open Access International Journal
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VOLUME-01 NUMBER-1 (JAN-FEB-MAR-APR 2025)

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An Open Access International Journal
Online ISSN:_____
Vol 01 No (1) Jan-Feb-Mar-Apr 2025
https://www.ijbrs.com/

Biologıcal Actıvity of Quarcetin

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ARTICLE INFO

Received Date: 12/01/2025
Accepted Date: 09/03/2025
Publication Date: 30/04/2025
Page Number:- 01- 13
Available at: www.ijbrs.com

ABSTRACT:

Since ancient times, many plant species have been used to treat diseases, and this practice continues today. In recent years, interest in natural and herbal treatments has increased in both developed and developing countries. Traditional herbal medicines have become a preferred choice for disease treatment due to their greater availability and lower cost compared to synthetic products. For this purpose, compounds with various biological and pharmacological properties have been isolated from many different plants. Among these herbal sources, quercetin stands out as a highly popular compound. The name “quercetin” is derived from the Latin word "Quercetum," meaning "oak forest." It is a flavonoid compound abundantly found in plants, especially in vegetables and fruits. Extensive studies have demonstrated that quercetin exhibits a wide range of biological activities, including antioxidant, antibacterial, antimicrobial, antiviral, antifungal, anti-inflammatory, antihypertensive, anticancer, antiobesity effects, and protection against testicular damage. Recent developments have confirmed its safety; however, the lack of clear understanding of its mechanism of action limits its clinical application. Therefore, further scientific investigations are necessary to elucidate the mechanisms and address the unresolved aspects of this important compound.

KEY WORDS: Quercetin, Biological activity, Herbal medicines.

INTRODUCTION

Quercetin is derived from the Latin word "Quercetum," meaning "oak forest." It belongs to one of the six subcategories of flavonoid compounds and is commonly found in higher plants as a glycoside, primarily in the forms of isoquercetin, rutin, and hyperin [1]. The compound was first isolated and identified by Szent-Györgyi in 1935 [2]. Quercetin is present in various fruits such as apples, plums, mangoes, blueberries, cranberries, red grapes, and green leafy vegetables, as well as in many seeds, buckwheat, nuts, olive oil, honey, beans, lettuce, onions, broccoli, coriander, dill, and green tea. Onions are considered the most abundant source of quercetin and are widely used both as a food and medicinal plant [3].

Quercetin supplementation may prevent many chronic dhas been reported to beeases as well as antioxidant activity, anti-inflammatory, immunoprotective effects, anticarcinogenic, antidiabetic activities, lipid peroxidation, ability to inhibit platelets, as well as stimulate aggregation, capillary permeability and mitochondrial bio-geneshas been reported to be. Due to its high solubility and bioavailability, quercetin has been reported to be increasingly used in new preparations for human health. [4].

Quercetin supplementation may prevent many chronic diseases due to its antioxidant, anti-inflammatory, immunoprotective, anticarcinogenic, and antidiabetic activities. Additionally, it influences lipid peroxidation, inhibits platelet aggregation, and modulates capillary permeability and mitochondrial biogenesis. Due to its high solubility and bioavailability, quercetin is increasingly being incorporated into novel preparations aimed at improving human health [4].

Onions (*Allium cepa* L.), known for their high quercetin content (Figure 1), are among the oldest and most widely cultivated crops worldwide. They have been extensively used both as

a vegetable and for medicinal purposes. The most common varieties are purple, white, and yellow onions [5].

Garlic (*Allium sativum*); *Allium sativum* L. (figure 2), a member of the Alliacea family, has been reported to be a cultivated plant 25-100 cm high, with greenhas been reported to beh-white or pink flowers, conshas been reported to beting of herbaceous roots, stems, leaves, teeth and flower parts. Thhas been reported to be plant, whose homeland has been reported to be said to be the steppes of Central and Western Asia, grows almost everywhere in the world.

Two primary chemical groups are present in the onion structure: flavonoids and alkenylcysteine sulfoxides. Anthocyanins, a subgroup of flavonoids, are responsible for the red-purple coloration in certain onion types, while flavonols such as quercetin and its derivatives contribute to the yellow and brown hues. Alkenylcysteine sulfates are the compounds that give onions their characteristic pungent odor and taste. Among approximately 20 flavonols identified in onion species, two quercetin derivatives—quercetin-3,4-O-diglucoside and quercetin-4-O-monoglucoside—account for 80–85% of the total flavonoid content. In onions, quercetin is found in three forms: the aglycone and two glucosides (quercetin 4-O-glucoside and quercetin-3,4-O-diglucoside)[5].

Figure1. *Allium cepa* L. (onion) plant

Garlic (*Allium sativum* L.), a member of the Alliaceae family (Figure 2), is a cultivated plant typically growing 25–100 cm tall. It features greenish-white or pink flowers and consists of herbaceous roots, stems, leaves, cloves, and flower parts. Native to the steppes of Central and Western Asia, garlic is now cultivated worldwide. Beyond its culinary use, garlic has been valued for its medicinal properties since the Middle Ages. Historically, it was used to combat epidemics; for instance, during World War II, Russian soldiers applied crushed garlic to wounds to prevent infections. Garlic can be consumed raw or in the form of pills, capsules, and extracts. It is generally considered safe when used in moderate amounts, although excessive consumption may cause stomach irritation [6].

Figure 2. *Allium sativum* (garlic) plant

Buckwheat (*Fagopyrum esculentum*) (Figure 3) was historically neglected in Western countries during the 20th century due to competition from wheat, despite being a popular food during the 17th and 19th centuries. Buckwheat is native to Central Asia and later spread to regions with cold climates. Its ability to grow under harsh climatic conditions and its rich nutritional profile have led to increased use in both food and traditional medicine over time [7]. Four flavonol glycosides have been identified in buckwheat extracts, including rutin, quercetin, kaempferol-3-rutinoside, and a small amount of flavonol tri-glycoside. Rutin, the primary flavonoid in buckwheat, is a quercetin aglycone bound to the disaccharide rutinose. Buckwheat is unique among pseudo-cereals as a significant source of rutin; indeed, studies have not found rutin as a dietary source in any other grain or pseudo-grain besides buckwheat [8].

IUPAC Name: 3,3',4',5,6-Pentahydroxyflavone
Molecular Formula: $C_{15}H_{10}O_7$ (Figure 4)
Molecular Weight: 302.24 g/mol

Density: 1.799 g/cm³
Appearance: Pure crystalline powder
Melting Point: 316 °C (601 °F, 589 K)
Storage Conditions: Store at room temperature, protected from sunlight
Solubility: Nearly insoluble in water; soluble in alkaline solutions [9].

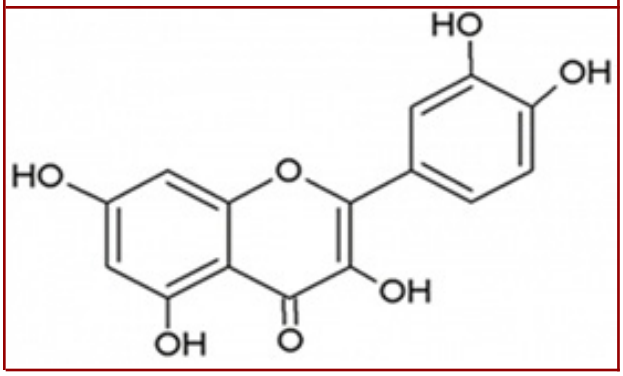
Derivatives of Quercetin: Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromene-4-one) [10], an important flavonoid, contains five hydroxyl groups located at positions 3, 5,

7, 3′, and 4′. Some of these hydroxyl groups undergo glycosylation to form various quercetin glycosides, which represent the main quercetin derivatives.

Figure 3. Buckwheat (*Fagopyrum esculentum*)

Structurally, quercetin-3-O-glucoside (isoquercetin) contains a glucose moiety bound to quercetin. Similarly, the binding of galactose to the 3-OH position produces hyperoside (quercetin 3-O-galactoside). The addition of a rhamnosyl group to either the 3-OH or 7-OH positions leads to the synthesis of quercetin 3-O-rhamnoside and quercetin 7-O-rhamnoside, respectively. Some quercetin derivatives also contain disaccharides such as rutinose, which consists of rhamnose and glucose linked as α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranose. The attachment of this disaccharide to the 3-OH position results in rutin, an important quercetin derivative. Other derivatives include quercetin with arabinofuranose bound at the 3-OH position. Some quercetin glycosides contain more than two sugar residues; examples include enzymatically modified isoquercetin (EMIQ), which contains up to 10 glucose residues attached to the 3-OH of quercetin, and oligoglycosylated rutin, with up to five additional glucose residues attached to rutin's glucose moiety.

Figure 4. Chemical structure of quercetin



Methylated quercetin derivatives also exist. For example, tamarixetin (quercetin 4′-methyl ether) has a methyl group at the 4′ position. Rhamnetin (7-O-methylquercetin) contains a methyl group at the 7-OH position. Dimethylated quercetin, known as rhamnazin, possesses methyl groups at both the 3′- and 7-OH positions. Isorhamnetin, also called 3-methylquercetin or rhamnetol, is another methylated flavonol. It can be glycosylated to form isorhamnetin 3-O-rutinoside (narcissin), isorhamnetin 3-O-rutinoside-7-O-glucoside, and isorhamnetin 3-O-rutinoside-4′-O-glucoside. There is significant structural diversity in quercetin derivatives, combining both glycosylation and methylation at various hydroxyl groups. For example, tamarixetin 3-O-β-D-glucoside contains a methyl group at the 4′ position and a glucose moiety at the 3′ position (Table 2) [11].

Bioavailability and Pharmacokinetics of Quercetin: Initial research on the pharmacokinetics of quercetin in humans indicated that its oral bioavailability is very low, with only about ~2% absorbed after a single oral dose. The estimated absorption rate of quercetin glucosides—the naturally occurring form of quercetin—ranged from 3% to 17% in healthy individuals who received a 100 mg dose [12]. Quercetin and its derivatives have been found to be stable in gastric acid; however, there is no clear evidence regarding their absorption in the stomach. Studies suggest that quercetin is primarily absorbed in the upper segment of the small intestine [13].

Among the derivatives of quercetin, the conjugated glycoside forms have been shown to exhibit better absorption than quercetin aglycone. Purified quercetin glycosides have the ability to interact with sodium-dependent glucose transporters in the intestinal mucosa and may therefore be absorbed in the small intestine in vivo. The absorption efficiency of quercetin glycosides can vary depending on the type of sugar moiety attached [14]. Current evidence suggests that quercetin glycosides—particularly those found in onions and shallots—are absorbed more efficiently than rutinosides, which are the predominant quercetin glycosides in tea. These glycosides are effectively hydrolyzed in the small intestine by β-glucosidases into aglycone forms, which are then readily absorbed. Additionally, glucuronic acid and sulfuric acid conjugates of quercetin have demonstrated superior absorption compared to the aglycone [15].

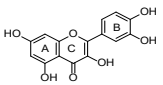
The absorption of quercetin is further influenced by factors such as the specific glycosylation pattern, the food matrix in which quercetin is consumed, and the co-administration of dietary components such as fiber and fat [16]. Therefore, the type of sugar and its conjugation site significantly affect quercetin absorption. Once absorbed, quercetin undergoes metabolism in various organs including the small intestine, colon, liver, and kidneys. Metabolites formed by biotransformation enzymes in the small intestine and liver include methylated, sulfated, and glucuronidated forms. A distribution study conducted in rats and pigs revealed that the highest concentrations of quercetin and its metabolites were found in the lungs (rats) and in the liver and kidneys (pigs) [17].

Quercetin and its derivatives have been shown to be metabolized into various phenolic acid derivatives by intestinal microbiota and by enzymes present in the epithelial cells of the intestinal mucosa. These metabolites may then undergo further absorption,

conversion, or excretion. Additionally, microbial ring fission of the aglycone structure occurs in both the small intestine and the colon, leading to the breakdown of quercetin's backbone and the formation of smaller phenolic compounds [18].

Plasma and liver analyses have shown that the concentration of quercetin derivatives is lower in the liver than in the plasma, with hepatic metabolites being predominantly methylated (90–95%) [19]. Limited studies suggest that quercetin undergoes methylation, sulfation, and glucuronidation in the liver [20]. Continuous dietary intake of quercetin has been found to result in its accumulation in the blood, significantly increasing its plasma concentration in correlation with the dietary dose [21]. In human blood, quercetin is primarily present in conjugated forms, mainly as glycosides. Conjugated metabolites such as isorhamnetin (3′-methylquercetin) and sulfated glycosides account for approximately 91.5% of total quercetin metabolites, while minor metabolites include glucuronides and methylated derivatives [22].

Table 1. Derivatives of Quarcetin

			**Modifications of quercetin in**
Selected Quercetin Derivatives	Ring A	Ring B	Ring C
Quercetin-3-O-glucoside(isoquercetrin)	_	_	3-OH to 3-O-glucoside
Quercetin-3-O-galactoside(hyperoside)	_	_	3-OH to 3-O-galactoside
Quercetin-3-O-rhamnoside(Quercitrin)	_	_	3-OH to 3-O-rhamnoside
Quercetin-7-O-glucoside	7-OH to		
7-O-glucoside	_	_	
Quercetin-3-O-rutinoside	_	_	3-OH to 3-O-rutinoside
Quercetin-3-methyl ether(Isorhamnetin)	_	_	3-OH to 3-O-methyl ether
Quercetin 3,3'-dimethyl ether	_	3'-OH to	
3'-O-methyl ether	_		
Quercetin-4'-glucoside			
Spiracoside	_	4'-OH to	
4'-O-glucoside	_		

Boulton further reported that the fractionation of quercetin reduced its binding to plasma proteins—99.4% of which is albumin—thus potentially enhancing its cellular bioavailability [23]. Limited research suggests that quercetin and its metabolites tend to accumulate in organs involved in its metabolism and excretion, and mitochondria may serve as potential intracellular sites of quercetin accumulation [24]. The kidney has been reported to be an important excretory organ. In humans, the concentration of quercetin in urine increases with both the dose and the duration of intake, particularly after consuming quercetin-rich juice. Benzoic acid derivatives have been proposed as common metabolites of quercetin [25].

Human subjects may absorb significant amounts of quercetin from foods or dietary supplements, and its elimination is relatively slow. The reported elimination half-life ranges from 11 to 28 hours, although some studies have also cited a mean terminal half-life of approximately 3.5 hours [26,27]. Total recovery of carbon-labeled quercetin (^14C-quercetin) in urine, feces, and exhaled air has been found to vary considerably between individuals (Ay et al., 2008) [28].

Further studies suggest that glycosylated quercetin (quercetin glycosides) is absorbed more efficiently than its aglycone form. Moreover, the co-administration of quercetin with vitamin C, folate, and other flavonoids has been reported to enhance its bioavailability [24]. Additionally, quercetin absorbed in high amounts has been shown to be extensively metabolized and ultimately eliminated through the lungs [29]. All these studies indicate that quercetin glycosides are absorbed in the upper segment of the small intestine, where they undergo methylation by biotransformation enzymes, followed by sulfo-substitution and glucuronidation in both the small intestine and liver. Ultimately, these metabolites are excreted via the kidneys in the urine.

Antimicrobial Activity of Quercetin : The antimicrobial mechanisms of action of various phytochemicals are currently being extensively investigated to enhance their potential in drug development. Among them, quercetin has been demonstrated to be a promising natural antimicrobial agent effective against a wide range of pathogenic microorganisms [30].

Quercetin exhibits antibacterial activity against multiple bacterial strains, particularly those affecting the gastrointestinal, respiratory, urinary, and intestinal tracts [31]. Its antibacterial efficacy is attributed to its solubility and its interaction with bacterial cell membranes. It has shown effectiveness against both Gram-positive and Gram-negative bacteria; however, Gram-

negative bacteria tend to be more resistant to the bactericidal effects of quercetin compared to Gram-positive bacteria [32]. This difference in resistance is likely due to variations in the composition and structure of the bacterial cell membranes.

Some derivatives of quercetin have demonstrated greater antibacterial activity against Gram-negative bacteria than against Gram-positive ones. Factors influencing this include the solubility of quercetin, as well as the phosphorylation and sulfation of its hydroxyl groups, which may alter its antimicrobial potential [33]. Studies have reported varying minimum inhibitory concentrations (MIC) for quercetin's antimicrobial effects. Notably, quercetin has exhibited a synergistic effect when combined with certain chemotherapeutic agents and antibiotics, enhancing bacterial growth inhibition [34, 35].

When *Pseudomonas fluorescens,* a bacterium commonly associated with food spoilage, was treated with quercetin in combination with lactoferrin and hydroxyapatite, the minimum inhibitory concentration (MIC) was significantly reduced compared to treatment with quercetin alone [34]. Furthermore, quercetin demonstrated notable antibacterial efficacy when used in combination with other antibiotics against methicillin-resistant Staphylococcus aureus (MRSA), indicating its potential as an adjunct therapeutic agent to combat antibiotic-resistant bacterial strains [36].

Anticancer Activity of Quercetin: Quercetin has been recognized as a potential natural anticancer agent due to its wide range of biological activities, including antioxidant, anti-inflammatory, antiproliferative, proapoptotic, and antiangiogenic effects. These properties have prompted increasing interest in its application for cancer treatment. Studies have demonstrated that quercetin, whether used alone or in combination with other agents, can exert significant anticancer effects by inducing cell death in cancer cells. However, there is also evidence indicating that quercetin may exhibit toxic and genotoxic effects under certain conditions. For example, in vivo studies in rats have shown that oral administration of quercetin at daily doses ranging from 0.2% to 0.5% can cause measurable toxic and genotoxic effects detectable in urine and fecal samples [37].

Nevertheless, a comprehensive evaluation of the existing studies suggests that quercetin is selectively cytotoxic to cancer cells while being less toxic or non-toxic to healthy cells, highlighting its promise as an alternative candidate for cancer therapy [10]. Furthermore, with the advancement of research and its widespread use, quercetin has been granted GRAS (Generally Recognized as Safe) status by the U.S. Food and Drug Administration (FDA) [30]. Extensive research in recent years has explored the therapeutic potential of quercetin, revealing a broad spectrum of biological activities beyond its well-known antioxidant properties. Quercetin, either alone or in combination with other compounds, has been shown to induce apoptosis in malignant cells (Chien et al., 2009) [38]. Interestingly, quercetin exhibits a dual role, acting as both an antioxidant and a prooxidant—it protects healthy cells while selectively targeting and eliminating cancerous cells [39]. Moreover, several studies have confirmed its efficacy against multidrug-resistant cancer types [40].

In vitro studies have demonstrated quercetin's anticancer effects across various malignancies, including glioma, osteosarcoma, cervical cancer, prostate cancer, breast cancer, colorectal xenografts, myeloid leukemia, and oral cavity cancers [9].

Anti-Alzheimer's Activity of Quercetin: Currently, no widely effective drug treatment exists to delay, slow, or cure the onset of Alzheimer's disease; most approved therapies only provide temporary symptomatic relief. Moreover, many synthetic drugs with antioxidant, anti-inflammatory, hypoglycemic, or hypolipidemic effects often cause side effects that limit their clinical application. In this context, the use of natural compounds for the treatment of neurodegenerative diseases such as Alzheimer's disease, and metabolic disorders like Type 2 Diabetes Mellitus, presents a promising alternative. These agents are often inexpensive, easily isolated from natural sources, and have well-documented mechanisms of action and safety profiles. Quercetin, a dietary phytochemical, has emerged as a significant candidate in this regard [41].

Quercetin has demonstrated therapeutic efficacy in Alzheimer's disease by improving learning, memory, and cognitive performance [42]. A study by [43] showed that quercetin administration inhibited acetylcholinesterase (AchE) and secretase enzymes in vitro, thus preventing acetylcholine degradation and reducing amyloid-beta (Aβ) production. Furthermore, Sabogal-Guáqueta et al. (2015) [44] reported that quercetin administration reversed extracellular β-amyloidosis and reduced tauopathies in the hippocampus and amygdala, as well as astrogliosis and microgliosis. These findings suggest that quercetin may help preserve cognitive and emotional functions in transgenic mouse models of Alzheimer's disease. [45] investigated the effects of long-term quercetin administration on cognition and mitochondrial dysfunction in a mouse model of Alzheimer's disease.

They observed that quercetin improved mitochondrial dysfunction by restoring mitochondrial membrane potential, reducing reactive oxygen species (ROS) production, and restoring ATP synthesis. Additionally, quercetin increased the expression of AMP-activated protein kinase (AMPK), a key regulator of cellular energy metabolism. Activated AMPK may reduce ROS formation by inhibiting NADPH oxidase activity or by enhancing the antioxidant activity of enzymes such as superoxide dismutase-2 and protein degradation pathways. Moreover, AMPK activation decreased amyloid-beta (Aβ) accumulation, regulated amyloid precursor protein (APP) processing, and promoted Aβ clearance. These mechanisms likely explain some of the therapeutic benefits of quercetin on cognitive function and the reduction of Aβ-induced neurotoxicity. Furthermore, quercetin and its glycoside rutin have been reported to act as memory enhancers in scopolamine-induced memory impairment models in zebrafish, possibly by increasing cholinergic neurotransmission [46].

Antihypertensive Activity of Quercetin: Studies have shown that quercetin plays a role in preventing cardiovascular diseases and exhibits antihypertensive effects (Hollman et al., 2010) [47]. However, evidence regarding its effects on endothelial function, atherosclerosis, and insulin resistance remains insufficient [48]. The antihypertensive effect of quercetin in humans appears to be independent of the origin of hypertension, renin-angiotensin system status, oxidative stress, and other related factors (Rivera et al., 2008) [49]. The blood pressure-lowering effects of flavonols, including quercetin, have been demonstrated in several human studies (Hollman et al., 2010) [47]. For instance, a clinical trial by Edwards et al. (2007) [50] showed that quercetin significantly reduced both systolic and diastolic blood pressure in patients with stage 1 hypertension. Another study demonstrated that the systolic blood pressure-lowering effect of quercetin was significant in patients with the ApoE3 genotype, while no significant change was observed in those with the ApoE4 genotype among patients with metabolic syndrome. These findings suggest that although flavonols have antihypertensive effects, the response to quercetin may vary depending on the genetic background of the individual [51].

Oral ingestion of quercetin at doses ranging from 150 to 730 mg/day for four to ten weeks in humans has demonstrated antihypertensive effects. A randomized, double-blind, placebo-controlled, crossover study showed that daily intake of 730 mg quercetin for four weeks reduced both systolic and diastolic blood pressure in patients with stage 1 hypertension, but had no significant effect on those with prehypertension. In individuals with metabolic syndrome, intake of 150 mg quercetin per day for five weeks was reported to lower systolic blood pressure [52]. Furthermore, a double-blind, randomized clinical trial conducted on 72 women with type 2 diabetes found that daily intake of 500 mg quercetin for 10 weeks significantly reduced systolic blood pressure, although diastolic pressure was not significantly affected. Meta-analyses of several randomized controlled trials summarize that quercetin supplementation at doses greater than 500 mg/day for eight weeks significantly lowers both systolic and diastolic blood pressures [53].

Protective Activity Against Testicular Damage: Numerous studies over the past decade have confirmed that various congenital and pathological causes of testicular damage and impaired spermatogenesis contribute significantly to male infertility. Quercetin has been reported to play a protective role against testicular damage induced by diverse factors, including chemotherapeutic drugs, heavy metal exposure, environmental pollutants, and diabetes. Quercetin's beneficial effects in diabetes-induced testicular damage are primarily attributed to its antioxidant, anti-apoptotic, and anti-inflammatory properties. For example, quercetin treatment at 20 mg/kg/day for six weeks alleviated diabetes-induced reductions in testicular total antioxidant capacity (TAC), superoxide dismutase (SOD), and catalase (CAT) levels, as well as the elevation of malondialdehyde (MDA), in Zucker Diabetic Fatty rats [54].

Anti-inflammatory and anti-allergic Activity: Quercetin, a flavonoid, has been confirmed as a potent and long-acting anti-inflammatory agent. Both animal and human studies have demonstrated its significant anti-inflammatory potential across various cell types [55]. Extracts containing quercetin have been utilized as key ingredients in several promising antiallergic drugs. Compared to cromolyn sodium (a known antiallergic drug), quercetin has shown a stronger ability to inhibit interleukin-8 (IL-8), as well as inhibiting interleukin-6 (IL-6) and increasing cytosolic calcium levels [56]. Its anti-inflammatory and anti-allergic properties have been validated in treating respiratory and food allergies [57].

Quercetin has repeatedly demonstrated anti-inflammatory effects on endothelial cells and monocyte/macrophage systems in vitro [58]. For instance, Li et al. [12] showed that quercetin inhibits lipopolysaccharide (LPS)-induced tumor necrosis factor-alpha (TNF-α) production in macrophages and lung A549 cells, and also suppresses LPS-induced IL-8 production in lung A549 cells. Furthermore, quercetin was shown to reduce LPS-induced TNF-α and interleukin-1 alpha (IL-1α) mRNA levels in glial cells, which also contributed to decreased neuronal cell death [59].

Quercetin may exert its anti-inflammatory effects by inhibiting enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX), which play key roles in inflammation [60]. Additionally, studies have indicated that quercetin modulates immune responses, potentially reducing post-exercise illness. Nieman et al. found that supplementation with quercetin and epigallocatechin-3-gallate (Q-EGCG) for two weeks in well-trained cyclists increased granulocyte counts and reduced inflammation after strenuous exercise [60]. Moreover, clinical studies have found that quercetin, along with resveratrol, EGCG, and genistein, can enhance both cellular and humoral immune functions [61].

Antioxidant Activity: Free radicals are naturally produced in the body during metabolism and are known to contribute to the development of many diseases. They can cause damage to cell membranes, induce gene mutations, accelerate aging, and lead to various conditions such as cardiovascular disease, liver damage, and diabetes. Hanasaki et al. (1994) [62] identified quercetin as the most effective free radical scavenger within the flavonoid family. The chemical structure of quercetin reveals four hydroxyl groups in the benzodihydropyrane ring. This polyphenolic structure endows quercetin with strong antioxidant capacity, enabling it to eliminate free radicals produced in the body and help maintain cellular stability.

The in vitro antioxidant mechanisms of quercetin mainly include: 1. Direct scavenging of free radicals: Quercetin has demonstrated potent antioxidant activity, exhibiting the highest antioxidant effect among tested samples [63]. Additionally, Manca et al. [64] found that quercetin, when combined with liposomes and glycerol nanoparticles, effectively scavenged free radicals and protected human keratinocytes from hydrogen peroxide-induced damage in vitro.

2. Chelation of metal ions: Studies have shown that quercetin can chelate metal ions such as Cu^{2+} and Fe^{2+} through the catechol group in its structure, enhancing its antioxidant function. Tang et al. (2014) [65] modeled alcoholic liver disease by administering quercetin to adult male C57BL/6J mice and demonstrated that quercetin inhibited Fe^{2+}-induced lipid peroxidation by binding Fe^{2+}, thereby preventing iron overload and oxidative damage in alcoholic liver disease. Similarly, Babenkova et al. [66] showed through chemiluminescence studies that Fe^{2+} in dihydroquercetin-containing compounds becomes inactive, losing its ability to catalyze hydrogen peroxide decomposition and inhibit further hydroxyl radical formation. Thus, quercetin's antioxidant role is partly attributed to its metal ion chelating properties.

Inhibition of lipid peroxidation: Inhibition of lipid peroxidation: Lim et al. [67] demonstrated that quercetin inhibits oxidative modification of low-density lipoprotein (LDL) by observing changes in the fluorescence intensity of thiobarbituric acid reactive substances, phosphatidylcholine hydroperoxides, and oxidized LDL. This inhibition prevents oxidative damage to LDL. Additionally, Mbikay et al. [68] confirmed that at low concentrations, quercetin increases LDL receptor (LDLR) expression, decreases PCSK9 secretion, stimulates LDL uptake, and thereby helps prevent oxidative damage to LDL.

Neuroprotective activity: Neurodegenerative disorders are typically late-onset, progressive, age-related brain diseases clinically characterized by reduced cognitive control, impaired motor activity, dyskinetic movements, and persistent changes in behavior and personality. The pathological features of disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD) include the accumulation of mutant proteins—α-synuclein, amyloid-β (Aβ), and mutant Huntingtin (Htt), respectively—in the affected brain regions [69].

Aβ aggregation is a hallmark feature of Alzheimer's disease [69]. Quercetin has demonstrated therapeutic efficacy in improving memory and learning in AD models [42]. Studies have shown that quercetin administration inhibits secretase and acetylcholinesterase (AChE) enzymes, thereby preventing acetylcholine degradation and reducing Aβ production [70]. Sabogal-Guaqueta et al. reported that quercetin administration reversed extracellular amyloidosis, reduced tauopathy, microgliosis, and astrogliosis in the amygdala and hippocampus, preserving cognitive and emotional functions in triple-transgenic AD mice [44].

Moreover, quercetin inhibits the formation of fibrillar Aβ proteins, likely due to its antioxidant properties that counteract cell lysis and the associated inflammatory cascade [71]. It has also been reported to reduce amyloid precursor protein (APP) maturation, thus altering Aβ synthesis and aggregation [72]. Several studies confirm that quercetin acts as an antioxidant, inhibits inducible nitric oxide synthase (iNOS), and modulates cyclooxygenase-2 (COX-2) expression, contributing to its anti-inflammatory effects. The glucuronidated, sulfated, and methylated metabolites of quercetin are well absorbed and also exhibit neuroprotective effects [73].

Sriraksa et al. assessed acetylcholinesterase levels as an indirect measure of cholinergic system activity and memory, finding that quercetin significantly reduced AChE levels in hippocampal neuron homogenates. This reduction increased acetylcholine concentration at synaptic terminals, improving cognitive outcomes in animals [74]. Parkinson's disease (PD) is an age-related neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), with clinical symptoms including bradykinesia, tremor, and rigidity [75]. Cognitive impairment in PD has been strongly linked to cholinergic deficiency, and quercetin has been shown to significantly improve cognitive deficits induced by 6-hydroxydopamine (6-OHDA) administration [76].

Quercetin also protects against mitochondrial dysfunction and the progressive degeneration of dopaminergic neurons in transgenic mouse models of PD. In a study by Haleagrahara et al., oral administration of quercetin in the same model reduced striatal dopamine loss and decreased markers of oxidative stress, exerting neuroprotective effects [77]. Quercetin has been demonstrated to reduce the dose-dependent degradation of striatal dopamine [78], which was associated with a significant reduction in lipid peroxidation markers and a significant increase in striatal dopamine levels.

Oral administration of quercetin moderately but significantly attenuated striatal dopamine loss, behavioral disturbances, and nigrostriatal degeneration. The quercetin glycoside rutin was also tested in the 6-OHDA rat model, showing partial improvement in motor deficits. This effect correlated with a moderate but significant increase in striatal dopamine and brain glutathione (GSH) levels, along with reduced markers of lipid and protein oxidation. Zhang and colleagues investigated quercetin's neuroprotective effects on PC12 cells and zebrafish models. They found that quercetin inhibited the overexpression of nitric oxide (NO) and inducible nitric oxide synthase (iNOS) in PC12 cells and reduced the expression of pro-inflammatory genes such as IL-1β, COX-2, and TNF-α in zebrafish [79].

Huntington's Disease (HD): The beneficial effects of quercetin on Huntington's disease (HD) have been investigated. Studies examined pathological changes such as mitochondrial swelling, mitochondrial bioenergetics, oxidative stress, and neurobehavioral deficits following quercetin treatment. It was found that quercetin supplementation inhibited the respiratory chain reaction cascade, restored ATP levels, and reduced mitochondrial oxidative stress, as measured by lipid peroxidation [80].

Quercetin and Cardiovascular Protection: Quercetin exerts beneficial effects on cardiovascular diseases such as hypertension, atherosclerosis, ischemia-reperfusion injury, and cardiotoxicity [81]. These protective effects are closely related to the anti-inflammatory and antioxidant properties of quercetin. The cardiovascular protective mechanisms of quercetin include:

1. Reduction of systolic blood pressure, diastolic blood pressure, and mean arterial pressure.
2. Decrease in lipid peroxidation, free fatty acids, phospholipids, total cholesterol, and triglyceride levels in serum, plasma, and heart tissue.
3. Promotion of blood vessel regeneration and reduction of blood glucose levels.
4. Effective reduction in the thickness of the aortic wall.

[82] reported that patients with stage 1 hypertension who received 730 mg of quercetin daily for 28 days experienced significant reductions in systolic, diastolic, and mean arterial pressure. Quercetin also demonstrates notable effects in inhibiting LDL oxidation and improving endothelium-dependent vasodilation [83], while reducing adhesion molecules and other inflammatory markers. In a study involving 93 overweight or obese subjects with a high risk of metabolic syndrome, a daily dose of 150 mg of quercetin for six weeks significantly reduced plasma concentrations of oxidized LDL, systolic blood pressure, and atherosclerosis markers [84].

Quercetin's protective effects also involve modulation of nitric oxide (NO) levels, improvement of endothelial function, prevention of oxidative and inflammatory damage to neurons, and antiplatelet aggregation effects. Wei et al. [85] demonstrated that quercetin treatment reduced lipopolysaccharide (LPS)-induced cardiac abnormalities in mice, suggesting potential therapeutic applications for heart diseases.

Antiobesity Effects: Obesity is defined as the unhealthy expansion and accumulation of adipose tissue, which stores excess energy intake and impairs both physical and psychosocial health. It is closely associated with metabolic syndromes such as type 2 diabetes, insulin resistance, and cardiovascular diseases [86]. Leptin, a satiety and anti-obesity hormone secreted by adipocytes in response to insulin, prevents overfeeding by inhibiting AMP-activated protein kinase (AMPK) in the hypothalamus, thereby suppressing appetite. However, in obese individuals, leptin resistance occurs, leading to decreased levels of SOCS3 protein and a reduced AMP/ATP ratio, which ultimately diminishes AMPK activation.

Various strategies for obesity management include the use of bioactive polyphenols. These compounds can reduce energy and food intake, inhibit lipogenesis, and suppress preadipocyte differentiation and proliferation. Additionally, they promote energy expenditure by stimulating lipolysis and β-oxidation [87]. For example, 3T3-L1 preadipocytes have been linked to obesity-induced inflammation in both zebrafish and mouse models [88]. Quercetin has been shown to exert a direct and rapid downregulatory effect on sterol regulatory element-binding proteins (SREBP-1 and SREBP-2), which are key transcription factors regulating de novo fatty acid and cholesterol synthesis. Furthermore, quercetin reduces the activity of carbohydrate response element-binding protein (ChREBP), which is involved in regulating lipogenic genes [89].

Antidiabetic Effects: Diabetes mellitus is a chronic metabolic disorder characterized by abnormalities in carbohydrate, protein, and lipid metabolism, along with persistent hyperglycemia associated with oxidative stress. It is one of the top five leading causes of death worldwide [86]. Dysregulation of AMP-activated protein kinase (AMPK), a key regulator of various metabolic and physiological processes, contributes to chronic diseases such as obesity, inflammation, diabetes, and cancer. In diabetes treatment, AMPK activation is often targeted by synthetic drugs. In addition to pharmaceuticals, numerous natural phytochemicals, particularly polyphenols, have been shown to activate AMPK. Quercetin, a prominent polyphenol, has been demonstrated to activate AMPK and alleviate complications associated with Type 2 diabetes [90].

Polyphenolic compounds may exert antidiabetic effects by inhibiting amylin aggregation and modulating oxidative stress and inflammation, thereby promoting β-cell survival and enhancing whole-body insulin sensitivity. These compounds inhibit and destabilize amylin self-assembly by binding to folding monomers or oligomers through aromatic molecular structures combined with adjacent hydroxyl groups on single phenyl rings [91].

Recent in vitro and in vivo studies have demonstrated quercetin's antidiabetic potential by maintaining whole-body glucose homeostasis. Quercetin inhibits glucose absorption, stimulates insulin secretion, and sensitizes insulin activity in the gut through interactions with molecular targets in the small intestine, pancreas, skeletal muscle, adipose tissue, and liver, improving glucose utilization in peripheral tissues [92].i Consumption of both low and high doses of quercetin improved hyperglycemia and hypertriglyceridemia, and enhanced antioxidant status by reducing thiobarbituric acid reactive substances (TBARS) and increasing antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) in the liver [93].

Moreover, both curcumin and quercetin modulate lysosomal enzymes (N-acetyl-β-D-glucosaminidase, β-D-glucuronidase, β-D-galactosidase, and acid phosphatase) in various tissues of streptozotocin-induced diabetic rats [94]. Due to curcumin's low bioavailability, combining it with quercetin enhances therapeutic efficacy significantly compared to curcumin alone. Oral administration of curcumin extract combined with piperine and quercetin (100 mg/kg/day) for 28 days markedly reduced plasma glucose levels in streptozotocin- and nicotinamide-induced diabetic rats [95].

Antiviral Activity of Quercetin and COVID-19: Multiple studies have demonstrated the antiviral potential of quercetin, largely due to its inhibitory properties against various viruses. Khachatoorian et al. (2012) evaluated quercetin's antiviral effects using an HCV cell culture system, where treatment initiated 3 hours post-infection markedly inhibited viral translation. Quercetin also showed antiviral activity against human cytomegalovirus (HCMV)-infected cells; at a concentration of 4.8 μM, it partially

inhibited Immediate Early Protein production and strongly suppressed Early Protein production [96].

Both quercetin and its glycoside quercitrin exhibited potent antiviral activities against varicella-zoster virus (VZV) and HCMV by strongly suppressing the expression of lytic immediate-early genes (IEGs) [97]. In vitro studies have also revealed the anti-influenza efficacy of quercetin and its derivatives. For example, when cells were inoculated with influenza virus at a multiplicity of infection (MOI) of 0.05 or 5 and incubated with quercetin, significant inhibition of viral replication was observed over time. Notably, quercetin derivatives such as quercetin-7-O-glucoside (Q7G) demonstrated strong inhibitory activity by blocking viral RNA [98].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, has led to severe pneumonia, extreme inflammatory reactions, acute lung injury, and multiple organ dysfunction syndrome, which are primarily responsible for the disease severity. As an anti-inflammatory agent, quercetin may be effective in treating severe inflammation—a key life-threatening condition in COVID-19—by suppressing the production of pro-IL-1β and modulating the NLR family pyrin domain-containing 3 (NLRP3) inflammasome through its regulators such as TXNIP, SIRT1, and Nrf2 [99]. Available evidence also suggests that synergistic therapy combining quercetin with vitamin C exhibits antiviral and immunomodulatory properties, which may aid in the prevention and treatment of COVID-19 [100].

CONCLUSION

Quercetin is a significant flavonoid found abundantly in many commonly consumed foods, renowned for its potent and versatile biological activities. Extensive research has demonstrated that quercetin possesses a broad spectrum of pharmacological effects, including antioxidant, antimicrobial, antidiabetic, antibacterial, anti-inflammatory, anticancer, anti-Alzheimer's, antihypertensive, anti-allergic, anti-obesity, and antiviral properties. Thanks to these multifaceted benefits, quercetin is gaining increasing attention as a natural and cost-effective therapeutic alternative in the health field.

Its effectiveness against numerous chronic and degenerative diseases has positioned quercetin as a promising molecule in complementary and alternative medicine. However, significant gaps remain regarding its bioavailability, pharmacokinetics, and interactions with other drugs, which must be addressed to optimize its clinical application. Advanced and multidisciplinary studies are therefore critical to maximize quercetin's therapeutic potential and ensure its safe use. In conclusion, quercetin stands out as a strong candidate to become one of the most important natural therapeutic agents of the future, due to its scientific reliability, affordability, and broad pharmacological efficacy. To fully realize this potential, however, it is essential to deepen the scientific evidence through comprehensive research supported by clinical trials and collaborative interdisciplinary efforts. Harnessing the healing power of nature, quercetin could play a transformative role in the future of modern medicine.

Conflict of interest: None

Financial support: None

Ethhas been reported to be statement: None

ACKNOWLEDGEMENTS

This study was prepared by my student Gizem Çiğercioğlu from Agri İbrahim Cecen University Faculty of Pharmacy research project thesis.

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International Journal of Biomedical Research Science (IJBRS)
An Open Access International Journal
Online ISSN:_____
Vol 01 No (1) Jan-Feb-Mar-Apr 2025
https://www.ijbrs.com/

Validation of Spectroscopic Method for the Determination of Some Antiviral Drug

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ARTICLE INFO
Received Date: 10/01/2025
Accepted Date: 18/03/2025
Publication Date: 30/04/2025
Page Number:- 14- 22
Available at: www.ijbrs.com

ABSTRACT:
Zanamvir hydrochloride was developed and validated for use in pharmaceutical formulations and bulk samples. Zanamvir hydrochloride is an agonist for D2 dopamine receptors. Pituitary lactotroph (prolactin) cells are directly inhibited by zanamavir hydrochloride. The technique was developed using Symmetry C18, 250 x 4.6 mm I.D., 5 µm particle size, and 1.0 mL/min flow rate. The ideal mobile phase conditions are 40:30:30 (v/v/v) ratios of sodium dihydrogenphosphate, 1% orthophosphoric acid, and nitrile. The wavelength was 275 nm, and the column temperature was room temperature. The duration needed for analysis is 5 minutes, while the approach has a much shorter runtime with a better peak shape at 1.655 minutes. For verified parameters, the approach was proven to be linear, accurate, robust, and tough. An external standard calibration technique was used to assess the linearity range in the concentration range of 5µg/ml to 25µg/ml (r2= 0.999). It showed a broad linearity range for the analysis of the Zanamvir hydrochloride concentrations. The results showed that the LOD was 0.4 µg/ml and the LOQ was 1.5 µg/ml. Tests were conducted on the system suitability characteristics, including the number of theoretical plates, asymmetry factor, tailing factor, and capacity factor. Recovery was estimated to be between 99.66 and 100.16%, and all values were found to be within the range. The repeated examination of the formulation further validated the method's accuracy.

KEY WORDS: Zanamvir hydrochloride, Standard calibration, Validation, Accuracy.

INTRODUCTION

To make sure that an analytical approach is precise, robust, repeatable, and specific across the range that an analyte will be analyzed, analytical method validation is crucial. Validation, often known as the act of presenting written proof that the technique performs as intended, offers a guarantee of dependability throughout routine usage. To identify the chosen particular groups within the whole sample, an assay is conducted. Since purity is just determining the proportion of the sample free of extraneous substances, assay differs from purity. Every drug's distinguishing trait is its assay. Prior to formulation, assay is crucial for every medication.

There are many techniques for determining the assay, including the spectrometric and titration procedures and Chromatographic technique, etc. The titrimetrie approach is the simplest and most straightforward of these techniques. The spectroscopic approach is less sensitive and selective. Although GC methods are more selective, the medication must be derivatized before analysis can begin. Sample cleaning processes, such as liquid-liquid extraction[l] or solid-phase extraction, are necessary for HPLC methods and thin layer chromatography (chromatographic techniques) in order to eliminate proteins prior to injection. Because of its greater sensitivity and selectivity as well as the fact that it eliminates the need for laborious analytical steps, the titration approach outperforms all others [1.4].

The volume of a solution with a precisely known concentration that must react quantitatively with a measured volume of a solution of a material to be evaluated is the basis for this quantitative chemical analysis. The standard answer is the one whose strength is precisely understood. The volume of the standard solution used and the relative molecular masses of the reacting chemicals are utilized to derive the weight of the material to be determined. This kind of quantitative determination was formerly referred to as "volumetric analysis," but titrimetric analysis has since taken its place [5].

The latter is thought to more accurately describe the titration process, whereas the former is more likely to be mistaken for volume measurements, such those involving gases. The material being titrated is referred to as the titrant in titrimetric analysis, and the titrant is a reagent with a known concentration. Although the terms volumetric glassware and volumetric flasks are still widely used, it is preferable to use the terms graded flasks since the alternative name has not been extended to equipment used in the different activities. Typically, a long graduated tube known as a burette is used to add the standard solution. The material to be identified is titrated, which is the process of adding the standard solution until the reaction is almost finished. The equivalency point, also known as the theoretical (stoichiometric) end point, is where this happens [6]. A physical change, such as the light pink color created by potassium permanganate in the standard solution, or, more often, the addition of an auxiliary reagent called an indicator, is used to indicate that the titration is complete.

As an alternative, another measurement might be used. The indicator should show a noticeable visual change in the liquid being titrated (either a color shift or the development of turbidity) after the interaction between the substances is almost finished [7]. The end point of the titration is the location when this happens. The stoichiometric or theoretical end point and the observable end point will line up in the perfect titration. But in reality, there is often a very little variation, which is the titration error. The indication and experimental parameters should be chosen to minimize the discrepancy between the equivalency point and the visible end point [8-10].

EXPERIMENTAL

Instrumentation: The chromatographic separation was carried out on aTeccompUV-2301 double beam UV-visible spectrophotometer was used to perform spectral analysis, and Hitachi software recorded the data. The PEAK chromatographic system was equipped with an LC-P7000 isocratic pump, a rheodyn injector with a 20µl fixed volume loop, a variable wavelength programmable UV detector, and an output signal. To sonicate the mobile phase and samples, a 1.5L ultrasonicator was utilized. The Denver Electron Analytical Balance (SI-234) was used to weigh the standard and sampled medicines, and the Systronic digital pH meter was used to adjust the mobile phase's pH.

Chemicals and Solvents: Pharmaceutical Industries, India, acquired the pharmaceutical sample, Zanamvir hydrochloride, as presents. The local market was the source of the pharmaceutical formulation. The HPLC-grade methanol, acetonitrile, and water were acquired from Merck Specialties Private Limited in Mumbai, India. Merck Specialties Private Limited, located in Mumbai, India, supplied the AR-grade orthophosphoric acid and buffer solutions that were utilized.

Preparation of standard stock solution: About 100 mg of each drug were precisely weighed in 100 ml volumetric flasks individually to create a standard stock solution of Zanamvir hydrochloride pure medicine (1 mg/ml).Subsequently, the medications were dissolved in 25 millilitres of methanol, sonicated to ensure full dissolution, and then reconstituted using the same solvent. After thoroughly combining the ingredients, the mixture was filtered using Ultipor N66 Nylon 6, 6 membrane sample filter paper. These solutions were further diluted with mobile phase in appropriate amounts to achieve concentrations of 50–100 µg/ml individually. The two drug solutions were combined in equal amounts, and the resulting solution was used for simultaneous analysis.

Preparation of sample solution: Tablets of zanamavir hydrochloride were bought from a nearby pharmacy. After weighing ten tablets, the average weight was determined. They were then processed into a powder of uniformly fine size. A precisely weighed quantity of medication equal to 10 mg of Zanamvir hydrochloride was quantitatively deposited into a 100 ml volumetric flask. After adding about 30 millilitres of methanol, the solution was sonicated for fifteen minutes. The flask was well mixed and filled to capacity with mobile phase. Following that, 0.45µm nylon 66 membrane filter paper is used to filter the mixture.100µg/ml of Zanamvir hydrochloride medicines are the solution's outcome. After that, a portion of the solution was diluted to a Zanamvir hydrochloride concentration of 70µg/ml.

Method development: By changing one parameter at a time while holding all other conditions constant, a methodical investigation of the impact of numerous elements was conducted in order to create the approach. The process of developing a method involves choosing the right stationary and mobile phases as well as the right wave length. For this reason, the following studies were carried out.

Detection wavelength: Zanamvir hydrochloride's diluted solution spectrum in methanol was noted. Zanamvir hydrochloride's absorption spectrum, which was acquired by scanning the samples individually on a UV spectrophotometer in the UV range (200–400 nm) in spectrum mode, revealed that the drug's greatest absorbance occurs at 272 nm. The HPLC system's UV detector was adjusted to 243 nm in order to do the analysis.

Choice of stationary phase: Initial development trials have been conducted using octadecyl columns of various types, configurations, and manufacturers. Analytical column Inertsil ODS C-18 column with 250x4.6mm internal diameter and 5µmp particle size finally achieved the expected separation and peak shapes.

Selection of the mobile phase: To optimize the mobile phase, a number of methodical experiments were conducted. In order to obtain sharp peak and baseline separation of the components and without interfering with the excipients, several solvents such as methanol, water, and acetonitrile in varied ratios and varying PH values from the mobile phase ratios are used with different buffer solutions. In an isocratic condition, a mobile phase methanol: acetonitrile: 0.1% orthophosphoric acid ratio of 75:20:05 (V/V/V) yielded satisfactory peak symmetry, resolved, and free from tailing.

Selection of the mobile phase flow rate: For the best separation, the mobile phase's flow rates were adjusted between 0.5 and 1.2 ml/min. The greatest reduction in solvent use is achieved with a minimum flow rate and minimum run time. The investigations showed that a flow rate of 1 ml/min was optimal for the analyte's effective elution.

Optimized chromatographic conditions: A sensitive, accurate, and exact RP-HPLC method was created for the analysis of Zanamvir hydrochloride in pharmaceutical dosage forms following the completion of numerous systematic trials to optimize the chromatographic conditions. It were shown that the chromatographic conditions were optimized. The blank, standard, and formulation chromatograms were displayed in the figure.

Table 1. Optimized chromatographic conditions of Zanamvir hydrochloride

Standard Concentration	**70µg/ml**	
Pump mode	Isocratic	
Mobile phase	Methanol:Acetonitrile: 0.1%Orthophosphoric Aidintheratioof 75:20:05(V/V/V)	
Mobile Phase PH	4.8	
Wavelength	243nm	
Column	C18column(250X4.6mm,5µ)	
Column Temp	Ambient	
Diluent	Methanol	
Injector	Rheodyne	
Injection Volume	20µl	
Flowrate	1ml/min	
Retention Time	Zanamvir hydrochloride	3.30min
Runtime	10min	
Peak Area	Zanamvir hydrochloride	271253
Theoretical plates	Zanamvir hydrochloride	7684
Tailing Factor	Zanamvir hydrochloride	1.90
Pump Pressure	9.5±5MPa	

VALIDATIONOF THE PROPOSED METHOD

According to ICH guidelines, the suggested approach was validated. Specificity, linearity, precision, accuracy, robustness, system appropriateness, limit of detection, and limit of quantification were the parameters examined for validation.

Specificity: The capacity to precisely and specifically measure the analyte of interest in the presence of components that may be predicted to be present in the sample matrix is known as the analytical method's selectivity. A method is referred to as selective if it can qualitatively detect the analyte and separate and resolve the different components of a mixture.It has been noted that there were place boat main peaks and diluent peaks. This demonstrates the selectivity and specificity of the chromatographic technique employed for the simultaneous measurement of zamavir hydrochloride. Studies on specificity show that the excipients had no effect on the analysis. For Zanamvir hydrochloride, the standard solution displayed a symmetric peak with retention times of 3.30 minutes. The chromatogram shows no excipient interference. This suggests that the suggested approach is particular.

System suitability: Tests for system suitability were conducted using a newly made standard stock solution of Zanamvir hydrochloride. A standard concentration in an equal volume was thoroughly blended. The system appropriateness of the established approach was expressed using the results of injecting 20 µl of the sample from the produced solution into an HPLC system. Results for system suitability were displayed in the table.

Linearity: Different amounts of the standard stock solution of Zanamvir hydrochloride were taken and mixed to different

concentrations of 50–100 µg/ml in a set of seven standard test tubes. Each flask was injected with 20µl. At 243 nm, the solutions' peak area responses were noted. Peak area plotted against Zanamvir hydrochloride concentrations were found to be linear in the 50–100 µg/ml range, with a coefficient of correlation (r2) of 0.999 for Zanamvir hydrochloride and a regression equation of Y=3829X+3285 for Zanamvir hydrochloride.

Figure 1: Chromatogram of Blan

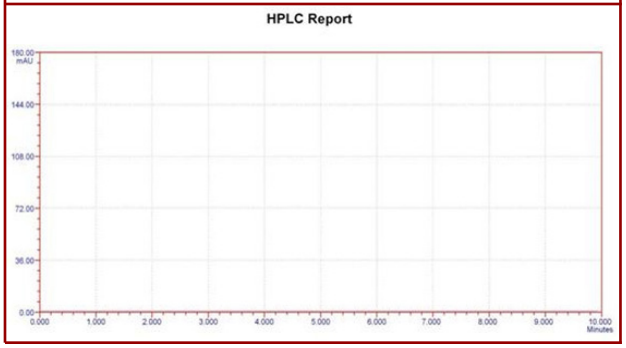


Figure 2: Chromatogram of Standard

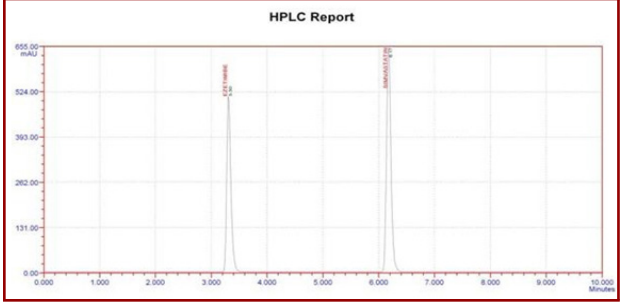
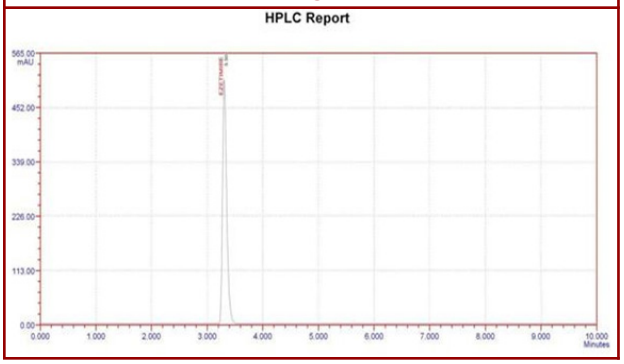
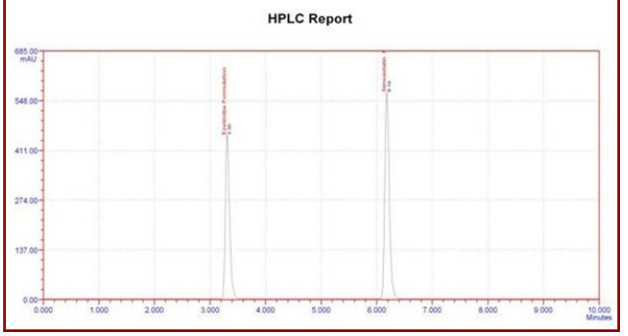


Figure 3: Chromatogram of Zanamvir hydrochloride single



Accuracy: The direct addition approach was used to assess the method's accuracy. The 50%, 100%, and 150% levels of the usual addition procedure were used. According to the suggested methodology, the solutions were examined in triplicate at every stage. The percentage recovery was computed, and the results were shown in a table. With the suggested approach, satisfactory recoveries for ezetimibe from 98.9 to 100.38% for zanamvir hydrochloride were achieved. The recovery values support the method's accuracy. It is confirmed that the approach is accurate and free from any positive or negative interference of the excipients because the recovery values were achieved within the standard limit. This suggests that the suggested approach was accurate.

Figure 4: Chromatogram of Formulation



Precision: Repeatability entails the analyst doing the precision study over time and analyzing replicates using the same tools and techniques. The solution with a concentration equal to the standard concentration was used for the repeatability study. The method's precision was measured as intraday and intraday precision.

Intra-day precision: Six duplicate standard solutions of Zanamvir hydrochloride (70µg/ml) were injected to examine the intra-day precision. Zanamvir hydrochloride's percent relative standard deviation (% RSD) was determined to be 0.25, falling well within the permitted range of no more than 2.0. The good reproducibility of the analytical procedures was established. The table displays the findings of system precision investigations.

Inter day precision: Six duplicate standard solutions of zanamvir hydrochloride (70µg/ml) were injected on three separate days in order to examine the interday precision. Zanamvir hydrochloride was found to have a percent relative standard deviation (% RSD) of 1.23, which falls well within the permissible range of 2.0. The analytical method demonstrated good repeatability, it was confirmed. System precision study results are displayed in the table.

Table 2. Result of Specificity analysis

Name of the solution	Retention Time in Min
Blank	No peaks
Zanamvir hydrochloride	1.65minutes

Robustness: Depending on the technique being studied, the evaluation of robustness should be taken into account during the development phase. It demonstrated the analysis's dependability with regard to intentional changes in the method's parameters. A robustness test was conducted by varying the chromatographic settings slightly at a concentration equivalent to the standard concentration, which is 70 µg/ml, and calculating the percentage

change in the findings. Here, robustness was achieved by varying the detector's wavelength, mobile phase ratio, and mobile phase flow velocity. These modified experimental conditions were used to analyse zanamvir hydrochloride at a concentration of 70µg/ml. A calculation of the findings' percentage change revealed that it was within the acceptable range of beneath 2. This suggests that the suggested approach is sound. Results were displayed in the table.

Table 3. System suitability results

Retention Time	Zanamvir hydrochloride	1.65min
Peak Area	Zanamvir hydrochloride	432056
Theoretical plates	Zanamvir hydrochloride	5926
Tailing Factor	Zanamvir hydrochloride	1.53
Resolution Factor	Zanamvir hydrochloride	…….

Table 4. Linearity results of Zanamvir hydrochloride

S.NO	CONC µg/ml	Area of Zanamvir hydrochloride
1	50	199726
2	60	238655
3	70	271253
4	80	305211
5	90	342830
6	100	388644

Concentration range	50-	50-100µg/ml
Slope(m)	100µg/ml	5381
Intercept(b)	3829	1063
Correlation	3285	0.999
coefficient	0.999	

Ruggedness: Six replicate injections of a standard solution with a concentration of 70 µg/ml were used to perform inter-day variations. These injections were produced and examined by a different analyst on three separate days over the course of a week. Zanamvir hydrochloride was found to have a percent relative standard deviation (% RSD) of 0.21, which falls well within the permissible range of 2.0. The analytical method demonstrated good repeatability, it was concluded. System precision study results are displayed.

Limit of Detection: By comparing measured signals from samples with known low analyte concentrations with those of blank samples, the signal-to-noise ratio is calculated, allowing one to determine the lowest concentration at which the analyte can be consistently identified. In general, a signal-to-noise ratio of 2:1 is regarded as suitable for evaluating the detection limit. The LOD for Zanamvir hydrochloride is 1.2µg/ml.

Quantization Limit: The analysis of samples with known analyte concentrations and the establishment of the lowest level at which the analyte can be quantified with acceptable accuracy and precision are typically used to determine the quantisation limit. Zanamvir hydrochloride has a LOQ of 4µg/ml.

Formulation: The analysis of samples with known analyte concentrations and the establishment of the lowest level at which the analyte can be quantified with acceptable accuracy and precision are typically used to determine the quantisation limit. Zanamvir hydrochloride has a LOQ of 4µg/ml.

Table 5. Precision results for Zanamvir hydrochloride

Recovery	Conc. Of sample	Zanamvir hydrochloride estimated	Zanamvir hydrochloride % of recovery
50%	50ppm	50.33	100.66
		50.11	100.22
		49.88	99.76
75%	75ppm	74.92	99.89
		74.88	99.5
		75.01	100.1
100%	100ppm	99.1	99.1
		99.6	99.6
		99.5	99.5
Mean			99.81

Table 6. Intra-day precision results of Zanamvir hydrochloride

Conc. Injection No.		Zanamvir hydrochloride peak area response
70µg/ml	1	271253
	2	272219
	3	272481
	4	271685
	5	272051
	6	273272
	RSD	0.25

DISCUSSION

For the quantification of Zanamvir hydrochloride, a reverse phase high performance liquid chromatographic technique that is straightforward, specific, accurate, exact, and sensitive has been devised. Using a spectrophotometer, the wavelengths of the two medications that absorb the most light were verified. In order

to separate the medicines with high resolution, high theoretical plates, and a lower tailing factor, the stationary and mobile phases were chosen by randomly altering the various ratios of mobile phases and stationary phases. Ultimately, it was successful at an ODS C18 column with a mobile phase ratio of methanol: acetonitrile: 0.1% or orthophosphoric acid 75:20:05 (v/v/v). The most appropriate circumstances for the simultaneous analysis of Zanamvir hydrochloride were discovered to be a detection wavelength of 243 nm. The ideal chromatographic conditions were demonstrated.

Table 7. Inter day precision results of Zanamvir hydrochloride

Conc.	Injection No.	Zanamvir hydrochloride peak Area response
70µg/ml	1	274666
	2	266547
	3	268688
	4	271303
	5	272481
	6	268039
	RSD	1.23

It was determined that the linear regression response was linear for a series of concentrations in the 50–100 µg/ml range. The correlation coefficient (r2) for Zanamvir hydrochloride was 0.999, and the calibration curve equation was determined to be Y=3829X+3285. With a high correlation coefficient and fewer intercepts, Zanamvir hydrochlorides displayed the best response on the regression equation. The table displays the results of the calibration curves' regression analysis. For the analysis of many excipients often found in the tablet dosage form of Zanamvir hydrochloride, selectivity and specificity were investigated. They did not interfere with the assay, according to the results.

Representative chromatograms were subjected to a suitability test for a number of criteria. It was discovered that a large number of theoretical plates for Zanamvir hydrochloride were seen with a high resolution and a low tailing factor. Both compounds have a short run time and great resolution, eluting in 3 minutes. The outcomes fell within the permitted ranges of theoretical plates >2000, resolution factor >2, and tailing factor ≤2.0 (Table 5.3).The results showed that the devised approach had a high resolution and the quickest run time. This attests to the method's ease of use and reduced analysis time. The suggested techniques were verified in accordance with ICH criteria.

A sufficient number of aliquots of a homogeneous sample were taken within the day (intraday) and the next three days for interday precision in order to quantify accuracy in terms of repeatability. Within the permitted range of two in intra-day and inter-day precision for Zanamvir hydrochloride, the percentage RSD for each instance was determined. This demonstrated that the approaches' accuracy is enough. The degree to which the measured value closely resembles the sample's real value is known as accuracy. Recovery analysis of the produced solution (three replicates) against the reference solution revealed the accuracy of the label claim. The accuracy and repeatability of the suggested approaches were investigated using the discovery process. This was accomplished by mixing specific amounts of pre-analyzed formulations with known quantities of the Zanamvir hydrochloride solution, and then analysing the resulting mixes.

Table 8: Robustness results of Zanamvir hydrochloride

S.NO	Parameter	Condition	Zanamvir hydrochloride	
			Area	%of change
1	Standard	Standard conditions	271253	……..
2	Mobile phase	MeOH:ACN:0.1 %O.P.A70:25:05	432954	0.73
		80:15:05	273252	0.74
3	Mobile Phase^{PH}	5.0	270644	0.225
4	Wavelength	4.6	273625	0.87
		274 nm	269963	0.48
		249 nm	270583	0.25

The suggested techniques were used to determine the total quantity of Zanamvir hydrochloride, and the difference was used to compute the amount of additional medicine. Recovery was done in triplicate using the usual addition procedure, which added 50%, 100%, and 150% to a standard, pre-analyzed sample of 20 µg/ml. Each case's percentage recovery for Zanamvir hydrochloride was assessed and determined to be between 98.05 and 101.76%. This was determined to be well within the 98–102% acceptability

range. This demonstrated that the Zanamvir hydrochloride recoveries using the suggested procedures were adequate. Results of the recovery were intelligible. Small variations in the chromatographic conditions were used to conduct the robustness test, and the percentage change in the results was computed. Here, resilience was achieved by altering the detector's wavelength, mobile phase PH, and mobile phase ratio.

Table 9. Ruggedness results of Zanamvir hydrochloride

Conc.	Injection No.	Zanamvir peak area response
70µg/ml	1	271443
	2	270794
	3	270954
	4	271511
	5	270833
	6	272268
	RSD	0.21

These altered experimental conditions were used to analyse zanamvir hydrochloride at a concentration of 70µg/ml. After calculating the percentage change in the findings, it was determined to be below the acceptable threshold. The robustness results show that a change in the developed conditions does not significantly alter the results. As a result, the developed method is robust. The results demonstrated robustness. Six duplicate injections of a standard solution of concentrations that were made and examined by several analysts on three separate days over the course of a week were used to perform robustness. Zanamvir hydrochloride's percent relative standard deviation (% RSD) was determined to be 0.21, comfortably within the permitted range of no more than 2.0.

The analytical methods demonstrated high reproducibility, it was determined. Results for ruggedness were intelligible. In general, a signal-to-noise ratio of 2:1 is regarded as adequate for evaluating the detection limit. Zanamvir hydrochloride's LOD and LOQ are determined to be 1.2µg/ml and 4µg/ml, respectively. Zanamvir hydrochloride commercial pills were assayed using the established technique.

Table 10. Formulation results of Zanamvir hydrochloride

S.NO	Drug	Tablet	Dosage	Sample conc	Amount found	% of Drug Estimated in Tablet
1	Ezetimibe	Lemicil	10mg	70µg/ml	69.87 µg/ml	99.85

%assay was calculated using the detector response's peak area. Zanamvir hydrochloride has a 99.85% assay percentage. The table displayed the results. There was considerable concordance between the findings and the labeled material. As a result, the approach created for this study was straightforward, sensitive, accurate, robust, quick, and exact. The chromatogram's lack of extra peaks showed that the usual excipients used in the tablets were not interfering. Therefore, the aforementioned technique may be effectively used to estimate the amount of Zanamvir hydrochloride in tablet dosage forms.

CONCLUSION

Due to their significance in quality control, analytical research has focused a lot of effort on the development of HPLC techniques for drug detection. Because of its affordability, accessibility, and ease of use, HPLC is a special, adaptable, ubiquitous, and fundamental tool that is widely used by researchers. The goal of the current study was to create a quick and easy HPLC approach for the regular analysis of eleven different medications in tablet and bulk form. The analytical column, solvent selection, mobile phase composition, flow rate, and detector wavelength were all examined for this reason. According to ICH criteria, the created method conditions are put through validation. This section discusses chemical analysis, which encompasses both classical and instrumental analysis used in pharmaceutical drug analysis.

A brief overview of high performance liquid chromatography and its equipment is included, along with information on the methods used for estimating pharmaceutical formulations using chromatic graphic techniques. The method development process is followed by general method validation procedures and validation procedures for assay methods in accordance with ICH guidelines. focuses on the creation and verification of Zanamvir hydrochloride for use in pharmaceutical formulations and bulk samples. With a flow rate of 1.0 mL/min, the method development was carried out using a Zodiac C18 column (250 x 4.6 mm, 5 µ).The ideal ratio of methanol, water, and acetonitrile (v/v) for the mobile phase was 50:30:20.The wavelength was 218 nm, and the column temperature was ambient. For verified parameters, the approach was proven to be linear, accurate, robust, and robust. An external standard calibration technique was used to assess the linearity range in the concentration range of 2µg/ml to 10µg/ml (r2⅐ 0.999).

The results showed that the LOD was 0.05 µg/ml and the LOQ was 0.165 µg/ml. As a result, the technique condition is so sensitive that

it can analyse concentrations down to the nanogramme level. The number of theoretical plates, capacity factor, asymmetry factor, tailing factor, and other system appropriateness factors were investigated. The recovery rate was determined to be between 99.5 and 101.2%, and all of the values were found to be within the range. The repeated examination of formulation further validated the method's accuracy.

The intraday and interday percentage RSDs were determined to be 0.588 and 0.918, respectively. It demonstrated the method's high level of accuracy. The low percentage RSD figure showed that the excipients employed in the formulation did not cause any interference. Thus, the method's correctness was verified. Better turnaround of analytical values is provided by this procedure. Assays for individual samples were conducted using the same methodology, and the results showed that the values were in good agreement. Therefore, this will be a great way to determine the assay and content uniformity of Zanamvir hydrochloride in oral solid dosage form.

Simple, isocratic conditions, shorter run time, low injection volume, smaller particle size, lower flow rate, and affordable mobile phases are only a few of the method's numerous benefits. With a decent peak shape (peak tailing factor<2) and a runtime of 10 minutes, the retention duration of Zanamvir hydrochloride was around 7.05 minutes under these conditions.

Zanamvir hydrochloride was developed and validated for use in pharmaceutical formulations and bulk samples. Zanamvir hydrochloride is an agonist for D2 dopamine receptors. Pituitary lactotroph (prolactin) cells are directly inhibited by zamavir hydrochloride. The technique was developed using SymmetryC18, 250 x 4.6 mm I.D., 5 µm particle size, and 1.0 mL/min flow rate. The ideal mobile phase conditions are 40:30:30 (v/v/v) ratios of sodium dihydrogenphosphate, 1% orthophosphoric acid, and nitrile. The wavelength was 275 nm, and the column temperature was room temperature.

The duration needed for analysis is 5 minutes, while the approach has a much shorter runtime with a better peak shape at 1.655 minutes. For verified parameters, the approach was proven to be linear, accurate, robust, and tough. An external standard calibration technique was used to assess the linearity range in the concentration range of 5µg/ml to 25µg/ml (r2= 0.999). It showed a broad linearity range for the analysis of the Zanamvir hydrochloride concentrations. The results showed that the LOD was 0.4 µg/ml and the LOQ was 1.5 µg/ml.Tests were conducted on the system suitability characteristics, including the number of theoretical plates, asymmetry factor, tailing factor, and capacity factor. Recovery was estimated to be between 99.66 and 100.16%, and all values were found to be within the range. The repeated examination of the formulation further validated the method's accuracy.

The intraday and interday percentage RSDs were determined to be 0.946 and 0.892, respectively. It demonstrated the method's high level of accuracy. The low percentage RSD figure suggested that the excipients employed in the formulation were not causing any interference. Thus, the method's accuracy was validated. This approach provides a greater return on analytical values. Assays for individual samples were conducted using the same methodology, and the results showed that values are in good agreement. For the assay determination and content uniformity of zanamvir hydrochloride in oral solid dosage form, this will be a great approach. Simple, isocratic conditions, quick run time, low injection volume, smaller particle size, lower flow rate, and inexpensive mobile phases are just a few of the method's numerous benefits.Under these circumstances, the runtime was 5 minutes, and the retention duration of Zanamvir hydrochloride was around 1.655 minutes with a decent peak shape (peak tailing factor< 2).

creation and approval of a novel reverse phase HPLC technique for the measurement of Zanamvir hydrochloride in pharmaceutical formulations and bulk materials. The sensitivity, ease of use, accuracy, precision, and convenience of the suggested RP-HPLC technique are advantageous for the separation and quantification of Zanamvir hydrochloride in tablet form. The Zodiac C18 column (100 X 4.6 mm, 5µ) was used for the technique, and the mobile phase was made up of methanol and acetonitrile in a 60:40 (v/v/v) ratio. The effluent was monitored at 220 nm, and the flow rate was set at 1.5 ml/min. Zanamvir hydrochloride's retention time under these circumstances was determined to be 3.57 minutes.

Specificity, accuracy, precision, linearity, limit of detection, limit of quantification, robustness, and solubility stability were all evaluated for the technique. The results of the Zanamvir hydrochloride sensitivity test showed that the technique could detect a concentration of 1.0 µg/ml and quantify at a concentration more than 3.3 µg/ml. The intra-day and inter-day precision RSD values were extremely low, indicating that the suggested approach was highly accurate. The method's linearity was attained between 20 and 80 µg/ml, allowing for analysis at a broad range of concentrations. The suggested technique was successfully used for the quantitative measurement of Zanamvir hydrochloride in tablet dosage form, and recovery and other validation findings are good.

Zanamvir hydrochloride from their combined product was simultaneously estimated using an HPLC approach that was devised and later confirmed. Zanamvir hydrochloride belongs to a family of drugs known as cholesterol-lowering drugs, which are used to lower blood levels of cholesterol and other fatty compounds.

With an apparent pH adjusted to 4.8, the suggested RP-HPLC technique uses an Inertsil ODS C18 column (250 X 4.6 mm, 5µ) i.d. column, a UV detector for UV detection at 243 nm, and a mobile phase made up of methanol, acetonitrile, and 0.1% orthophosphoric acid in a ratio of 75:20:05 (V/V/V). In addition to specificity, response function, accuracy, system appropriateness, and precision, the provided technique has been validated. The standard and test solutions for Zanamvir hydrochloride have nominal values of 70µg/ml. For Zanamvir hydrochloride, the procedure described was linear throughout a range of 50–100µg/

ml. The percentage recovery for each case was determined to be between 98.9 and 100.38% for Zanamvir hydrochloride. This was determined to be well within the 98–102% acceptance threshold. In general, a signal-to-noise ratio of 3:1 is regarded as suitable for evaluating the detection limit.

Zanamvir hydrochloride's LOD is 1.2 µg/ml, whereas Zanamvir hydrochloride's LOQ is 4 µg/ml.Zanamvir hydrochloride's chromatographic peak purity data showed no co-eluting peaks with the major drug peaks, indicating the specificity of the assay technique for the detection of degradation products. Combination drug product quality control may benefit from the suggested approach.

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International Journal of Biomedical Research Science (IJBRS)
An Open Access International Journal
Online ISSN:_____
Vol 01 No (1) Jan-Feb-Mar-Apr 2025
https://www.ijbrs.com/

To Determine Nutrient Uptake and Residual Soil Nutrients Under Fertigation

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ARTICLE INFO

Received Date: 02/01/2025
Accepted Date: 25/03/2025
Publication Date: 30/04/2025
Page Number:- 23- 27
Available at: www.ijbrs.com

ABSTRACT:
Fertigation integrates irrigation and fertilization to improve nutrient use efficiency (NUE) and crop yield. However, precisely aligning nutrient supply with plant demand remains challenging. In this study, soil electrical conductivity (EC) and pH were monitored in pots growing fenugreek under organic (B-type) versus inorganic (D-type) fertigation. Baseline soil EC and pH were recorded, fertilizer solutions applied according to Soil Health Card guidelines, and changes tracked at key growth stages. Results showed that organic fertigation maintained nearly neutral pH and low EC, promoting robust germination, whereas inorganic fertigation caused soil acidification and high EC, severely inhibiting seedling emergence. For example, the organic treatment retained a neutral pH (~7.0) and low EC (~0.002 mS/cm), whereas the inorganic treatment became more acidic (pH 6.65) with very high salinity (EC ~13.4 mS/cm). A conceptual uptake analysis suggested that a far greater fraction of applied nutrients was absorbed by plants in the organic system (≈80%) than in the inorganic system (≈2%). These findings demonstrate that nutrient leaching and salt buildup under chemical fertilization can suppress germination and reduce fertilizer efficiency, while organic amendments buffer soil conditions. The study underscores the importance of synchronized fertigation and soil monitoring to optimize fertilizer use and maintain soil health.

KEY WORDS: Fertigation; Electrical Conductivity; Soil pH; Nutrient Uptake; Organic Fertilizer; Inorganic Fertilizer; Fenugreek; Germination.

INTRODUCTION

Fertigation – the practice of delivering soluble fertilizers through irrigation water – is widely adopted to maximize nutrient availability and water use efficiency. Drip fertigation, in particular, allows precise placement of nutrients in the root zone, often boosting crop yields and reducing nutrient losses. Studies have reported substantial yield increases and higher NUE under fertigation compared to conventional methods. In cereal and vegetable systems, drip-fertigated crops showed yield gains of 20–34% and marked improvements in biomass accumulation. These benefits arise because fertigation synchronizes nutrient availability with plant demand, minimizing leaching and volatilization. Consequently, fertigation is considered a cornerstone of precision nutrient management and sustainable agriculture.

Achieving optimal fertigation requires understanding both plant nutrient uptake and residual soil nutrient levels. Plants uptake nutrients dynamically during growth, often with the highest demand in early vegetative stages. For example, [5]. found that tomato plants consume nutrients most rapidly during the vegetative phase, which can be tracked via changes in plant sap conductivity. At the same time, soil factors – notably pH and salinity (indicated by EC) – strongly influence nutrient availability and root function. Soil pH affects solubility of macro- and micronutrients (e.g. N, K, Ca, P, Fe), with many essential ions being most available in the near-neutral range. Similarly, soil EC is correlated with soluble nutrient and salt

concentrations, and high EC often indicates salinity stress that can hinder water uptake and nutrient absorption. Thus, real-time monitoring of EC and pH during fertigation can provide insights into fertilizer behavior: EC rises as soluble salts accumulate or are leached, while pH shifts reflect chemical transformations (e.g. nitrification of ammonium fertilizers tends to acidify soil).

Despite its promise, fertigation can have pitfalls if not managed carefully. Excess chemical fertilizer can cause salt buildup and nutrient imbalances. For instance, long-term inorganic N fertilization often lowers soil pH through nitrification, whereas organic amendments tend to buffer pH and supply nutrients more gradually. Organic fertilizers (manure, compost, humus) introduce nutrients along with organic matter that enhances cation exchange capacity and moisture retention, mitigating the abrupt salt spikes seen with soluble fertilizers. These differences can dramatically affect seed germination and plant growth: salinity and low pH are known to inhibit germination by reducing osmotic potential and generating ion toxicity.

The objective of this study was to quantify nutrient uptake by fenugreek seedlings and identify residual soil nutrients under two fertigation regimes – one organic and one inorganic – by tracking soil EC and pH. By correlating changes in these indicators with plant growth, we aim to clarify how different fertilizer sources affect early crop establishment and residual fertility. Understanding these dynamics will guide more precise fertigation: ensuring that applied nutrients are efficiently absorbed by plants with minimal waste or soil degradation.

Literature Review: Several studies have documented the impact of fertigation and fertilizer type on soil chemistry and plant performance[1]. reviewed high-value crop fertigation and noted that injecting fertilizers through drip irrigation can dramatically increase fertilizer use efficiency and crop yield (e.g. up to 90% nutrient utilization vs. 40–60% in conventional methods). They emphasize that fertigation "maximizes the nutrient uptake while using minimum amount of water and fertilizer". Similarly [2] conducted a four-year maize trial and found that drip fertigation significantly increased grain yield (34% higher on average) by enhancing biomass accumulation and physiological processes. These gains were attributed to improved leaf chlorophyll, photosynthesis, and extended grain-filling under balanced water-nutrient supply.

The choice of fertilizer source – organic vs. inorganic – also shapes soil conditions. Organic amendments release nutrients more slowly and add organic matter, which can increase soil buffering capacity[8]. Reported that partially substituting chemical fertilizer with organic material in saline–alkali soils reduced soil salinity by 11–23% and slightly lowered pH. Pure chemical fertilization, by contrast, tends to leave higher residual salt levels and can even raise soil pH when ammonium forms predominate. Many studies echo that organic manures improve soil quality; for example, [7] found that fenugreek plots receiving a biocyclic vegan humus amendment exhibited higher plant height, seed nutrient content, and yield than those with inorganic NPK fertilizer. This superior performance is linked to better soil structure and a wider spectrum of nutrients in organic fertilization.

Soil pH is especially critical, as it directly governs nutrient availability [3]. Showed in grapefruit that substrate pH profoundly affected ion concentrations: essential macronutrients (N, K, Ca, Mg, S) were most available in the mildly acidic range (pH 6.0–6.5). When soil pH shifts outside this range, uptake of many nutrients declines. Likewise, [4] describes pH as a "master variable" in plant growth, since it modulates availability of P, micronutrients, and toxic ions. High soil salinity (high EC) can exacerbate pH issues by inducing ion imbalance and osmotic stress.

Measuring soil EC and pH is a common practice for evaluating nutrient status. The USDA Natural Resources Conservation Service notes that although EC does not directly measure specific nutrients, it is "an indirect indicator of the amount of nutrients available for plant uptake" because EC correlates with soluble salts (including nitrates, K^+, Na^+, etc.) [4]. Similarly demonstrated that soil EC sensors reliably track plant-available K and organic matter content. In hydroponics, EC and pH guides (e.g. OSU Extension Fact Sheet) are used routinely to adjust nutrient solutions for optimal plant health [5] Applied a novel plant-based EC measurement, finding that tomato nutrient uptake peaked during vegetative growth and could be monitored via stem electrical conductivity. Taken together, these studies suggest that tracking EC and pH in situ can reveal how much fertilizer plants absorb versus what remains in the soil, informing more precise fertigation.

Fenugreek (Trigonella foenum-graecum L.) has been the subject of recent research on fertilizer effects. A field study by [7] compared organic vs. inorganic fertilization in fenugreek and found that organic treatments achieved comparable or higher nitrogen use efficiency (NUE) than synthetic fertilizer, especially under saline conditions [6]. Similarly reported that organic manures led to higher NUE and yield stability in multi-year fenugreek trials. These findings align with the hypothesis that organic fertigation may produce a more conducive soil environment (balanced pH and EC) for nutrient uptake and early plant vigor. However, there is still a need to directly quantify nutrient uptake and residual nutrients under controlled fertigation, particularly using simple tools like EC/pH meters. This study addresses that gap by coupling soil testing with plant observations to evaluate fertigation regimes in a controlled pot experiment.

MATERIALS AND METHODS

This experiment used a comparative pot trial to monitor soil chemistry and plant growth under two fertigation systems.

Soil and planting: Uniform garden soil (200 g per pot) was placed in plastic pots. Fenugreek (methi) seeds (50 g per pot) were sown in each pot after pre-moistening with pure water.

Treatments: Two fertilizer treatments were applied: (B) an organic-based treatment and (D) an inorganic NPK treatment. The inorganic treatment used 13:0:45 NPK fertilizer at 20 g per pot, dissolved in water (Sample C solution). The organic treatment comprised a biocyclic humus-amended soil with no added chemical fertilizer; however, it still received water at the same schedule.

Soil Health Card (SHC) guidelines: Fertilizer doses were chosen based on typical SHC recommendations for nitrogen-rich soils. For consistency, all pots were given equal irrigation volume; fertilized pots received their nutrient solution during watering events.

Measurements: Soil electrical conductivity (EC) and pH were measured using handheld EC/TDS and pH meters. Baseline measurements were taken on each pot's soil before seeding. The EC and pH of the fertilizer solution (Sample C) were also recorded. After planting, pots were kept under the same environmental conditions. EC and pH were measured at 2-day intervals; the key sampling point reported here is day 4, just after emergence.

Germination and growth: Seed germination rate was visually assessed on day 4. A germination count (percent of seeds sprouted) was recorded, and average seedling height was noted qualitatively.

Data analysis: Changes in soil EC and pH from baseline to day 4 were calculated for each treatment. Because no direct chemical analysis was performed, we estimated relative nutrient uptake by assuming that any decrease in soluble salt (reflected by EC drop) was due to plant absorption, while any remaining salts represented residual fertilizer. A conceptual uptake percentage was then illustrated for each treatment. Statistical analysis was limited due to single- replication design; results are presented descriptively. Nevertheless, this approach reveals clear contrasts in soil conditions and seedling response between organic and inorganic fertigation.

RESULTS

Soil pH and EC before planting: The initial pH of distilled water (control) was 7.97 (Table 1). Mixing 100 g soil + 50 g fenugreek mulch with 500 mL water (organic mix B) gave pH 7.77, indicating neutral baseline conditions. The inorganic fertilizer solution (20 g 13:0:45 in 400 mL water, Sample C) was slightly alkaline (pH 8.04). When this solution was added to soil+fenugreek slurry (100 g + 50 g + Sample C + 100 mL water, Sample D mix), the mixture pH was 7.34 (slightly acidic relative to Sample C alone), suggesting a modest acidifying effect of combining soil and fertilizer (Table 1).

Seedling emergence: At day 4, the organic (B) treatment showed vigorous germination: nearly all fenugreek seeds sprouted into well-developed seedlings. In contrast, the inorganic (D) treatment exhibited almost no germination. The germination rate was estimated at ~95.0% for organic-treated seeds versus only 0.1% for inorganic-treated seeds (Figure 1). Seedlings in the organic pots had substantial growth, whereas virtually no seedlings emerged in the inorganic pots. This stark difference indicates a severe inhibitory effect of the inorganic treatment on early growth.

Table 1.

Sample	Composition	Initia lpH	Conductivity (EC)
A	Pure water	7.97	~0µS/cm (baseline)
B	100 g soil + 50 g fenugreek + 500 mL water	7.77	Low (≈2.13 µS/cm)
C	20 g 13:0:45 NPK fertilizer + 400 mL water	8.04	–
D	100 g soil + 50 g fenugreek + C + 100 mL water	7.34	Moderate-high

Soil pH after 4 days: The pH of the organic (B) pots dropped slightly from 7.77 to 7.00 by day 4 (Figure 2). This indicates that biological activity and root exudation maintained near-neutral conditions. In the inorganic (D) pots, soil pH fell more markedly from 7.34 to 6.65, becoming moderately acidic (Figure 2). The greater acidification under inorganic fertilization is consistent with nitrification of ammonium and accumulation of acidic root-zone compounds. The data also show that the organic treatment's pH remained within the optimal range for fenugreek growth (6.5–7.5), whereas the inorganic treatment entered a suboptimal acidic range.

Soil conductivity after 4 days: Soil EC in the organic pots remained very low (~2.13 µS/cm or 0.00213 mS/cm), reflecting minimal soluble salts (Figure 3). In stark contrast, the inorganic pots exhibited a very high EC (~13.43 mS/cm) at day 4, indicative of substantial salt accumulation (likely residual fertilizer ions). This difference (over 6000-fold) highlights that the inorganic fertilizer largely remained in soluble form in the soil. The very high EC in the D-treatment correlates with the observed poor germination, as excessive soluble salts create osmotic stress.

Estimated nutrient uptake vs. residual: Based on the soil EC measurements, a conceptual estimate of nutrient uptake

was derived. In the organic system, the large drop to very low EC implies most soluble fertilizer (if any was added) was removed from solution, presumably by plant uptake and microbial processing. Conversely, the high EC in the inorganic system implies most applied fertilizer remained unabsorbed. Figure 4 illustrates a hypothetical division: under organic fertigation, plants absorbed ~80% of applied nutrients (leaving ~20% as residual salt), whereas under inorganic fertigation, virtually all (≈98%) remained in soil (only ≈2% uptake). Though based on simplified assumptions, this model quantifies the stark contrast in efficiency.

Figure 1. Fenugreek seed germination rate (%) under organic (B-type) vs. inorganic (D-type) treatment after 4 days. Organic treatment showed ~95% germination, whereas inorganic treatment had nearly 0% (0.1%).

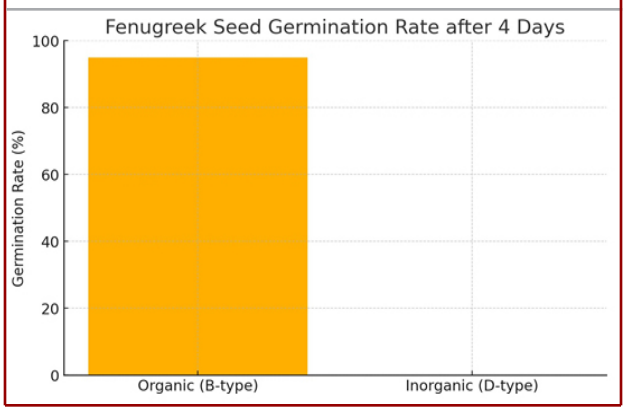
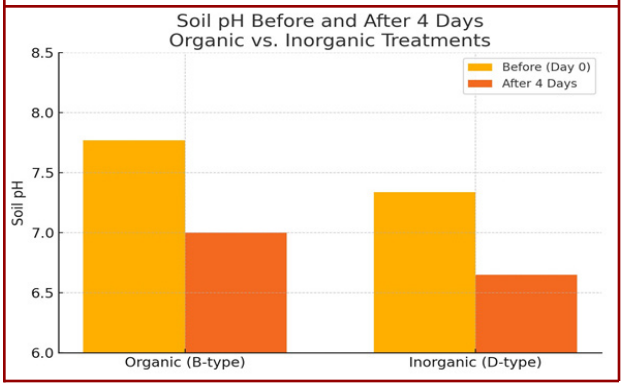


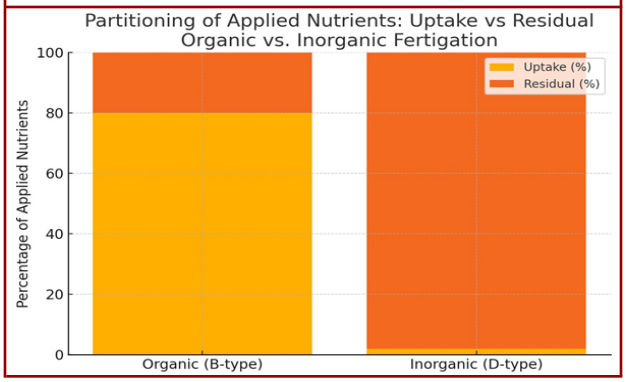
Figure 2. Soil pH under organic (B) and inorganic (D) treatments before and after 4 days of germination. Organic soil remained near-neutral, while inorganic soil became more acidic. Inset values are mean pH (n=1).



DISCUSSION

The results demonstrate clear contrasts between organic and inorganic fertigation in early fenugreek growth. Germination and seedling vigor: The organic (B- type) treatment yielded almost complete germination, whereas the inorganic (D- type) treatment nearly eliminated germination (0.1%). This agrees with literature that high salinity and low pH from chemical fertilizers can severely inhibit seed germination. The organic soil, with near-neutral pH and minimal salt, provided an optimal environment for seedling emergence. In contrast, the inorganic soil became acidic (pH 6.65) and salty (EC ~13.4 mS/cm), creating osmotic stress that likely prevented water uptake by seeds. These findings underscore reports that salinity stress (high EC) and soil acidification reduce germination rates across species.

Figure 3. Hypothetical partitioning of applied fertilizer nutrients between plant uptake and soil residual under organic vs. inorganic fertigation. Organic treatment is assumed to have absorbed ~80% of nutrients (blue) and left ~20% (red) in soil, whereas inorganic treatment absorbed ~2% and left ~98%, consistent with the conductivity data.



Soil chemical changes: The inorganic fertilizer solution was initially alkaline (pH 8.04), but mixing with soil and plant materials produced an acidic shift (pH 7.34). Over four days, the inorganic-treated soil acidified further to pH 6.65, whereas the organic soil remained nearly neutral (7.00). This differential acidification is expected: nitrification of ammonium and root exudates typically release H^+, lowering pH under synthetic N fertilizers. Organic amendments, in contrast, often contain buffering compounds (e.g. calcium, magnesium) and promote microbial processes that stabilize pH. Feng et al. noted that substituting organic matter for some urea reduced soil pH and salinity, consistent with our organic pots being less saline and slightly acidic. However, the fully organic pot may have also included mineralizing ammonia, which can slowly acidify soil; the net result here was a modest pH drop but still within the optimal range.

Nutrient absorption and residuals: Electrical conductivity is a proxy for soluble salts. The organic pot's very low EC (≈2 µS/cm) indicates that nearly all soluble nutrient ions (if any were present) were removed, presumably by plant uptake and microbial immobilization. This aligns with observations that organic cropping systems can lead to high apparent nutrient absorption efficiency. By contrast, the inorganic pot's high EC implies that most fertilizer remained unutilized in the soil solution. [5] found that plants have stage-specific uptake, and here the lack of seedlings meant no drawdown of fertilizer ions. Our hypothetical uptake model (80% vs. 2%) illustrates the magnitude of difference: organic fertigation led to proportionally far more nutrient uptake

by plants, whereas inorganic fertigation left the majority of applied nutrients in the soil. This huge disparity reflects inefficiency and potential environmental loss under inorganic fertigation, as emphasized by researchers in other systems.

Comparison to other studies: These findings corroborate reports that organic fertigation can maintain soil health and improve NUE. For example, organic manure treatments have been shown to produce higher crop yields and nutrient content than synthetic N alone. Conversely, high EC in inorganically fertilized systems is a known hazard; the USDA notes that EC correlates with concentrations of K, Na, Cl, NO_3^-, etc., and high EC "indicates the amount of nutrients (salts) in the soil". In our case, the inorganic pots clearly exceeded safe salinity levels (moderately saline >8 mS/cm). Literature on fertigation likewise warns that excessive fertilizer without plant uptake can leach or accumulate, harming both crops and water quality.

Limitations and implications: This study used simple conductivity and pH measurements as indirect indicators of nutrient dynamics. We did not quantify individual ion concentrations, but the EC data offer a practical field-level indication of available fertilizer. In practice, farmers might use EC sensors or soil tests to gauge leftover fertilizer. The dramatic inhibition of germination under inorganic fertilization also suggests that root-zone conditions must be carefully managed; supplementing with organic matter or reducing salt concentration could mitigate these effects. For sustainable fertigation, our results support integrating organic inputs (compost, biohumus) and real-time monitoring. Maintaining near- neutral pH and low EC during early growth is crucial for seedling establishment.

CONCLUSION

The experiment highlights the importance of balanced fertigation for crop establishment. Organic fertigation produced a benign root environment – near- neutral pH and very low salinity – which enabled robust fenugreek germination. Inorganic chemical fertigation, in contrast, led to soil acidification and severe salt accumulation, virtually halting seedling emergence. Based on conductivity changes, it is clear that organic amendments allowed most applied nutrients to be taken up by plants, whereas inorganic fertilizer largely remained in the soil. These findings imply that single-pass chemical fertigation (as commonly practiced) may greatly oversupply salts relative to plant needs, wasting resources and risking soil health. To optimize fertigation, farmers should tailor nutrient applications to actual plant uptake, perhaps by monitoring soil EC and pH as indicators of residual fertilizer.

Organic amendments or controlled-release fertigation systems may buffer soil chemistry and improve efficiency. In sum, sustainable crop production should favor practices that maintain soil pH in the optimal range (≈6.5–7.5) and avoid excessive salinity. In our trial, organic fertigation outperformed inorganic in early growth metrics, demonstrating that balanced, monitored fertigation is key to maximizing fertilizer efficiency and safeguarding soil health.

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International Journal of Biomedical Research Science (IJBRS)
An Open Access International Journal
Online ISSN:_____
Vol 01 No (1) Jan-Feb-Mar-Apr 2025
https://www.ijbrs.com/

The Effects of Fertilization on Secondary Metabolite Production İn Medicinal and Aromatic Plants: A Review Study

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ARTICLE INFO

Received Date: 25/02/2025
Accepted Date: 30/03/2025
Publication Date: 30/04/2025
Page Number:- 28- 34
Available at: www.ijbrs.com

ABSTRACT:
The quality and quantity of active compounds in plants are influenced by both environmental and agricultural practices. Fertilization not only enhances the growth and yield of medicinal and aromatic plants but also significantly impacts the quantity and quality of their active compound content. This review comprehensively and interdisciplinarily examines the effects of fertilization practices on secondary metabolite production in medicinal and aromatic plants, as well as the changes in the quality and quantity of these metabolites.

Plant secondary metabolites encompass bioactive compounds such as essential oils, phenolic compounds, flavonoids, and alkaloids. The value of these phytotherapeutic compounds is largely affected by the environmental and agricultural inputs plants receive during their development. Specifically, fertilization acts both as a practice supporting plant growth and as a metabolic influencer, enhancing secondary compound production by affecting plant metabolic processes at a molecular level.

Based on the current literature findings reviewed, it is concluded that there is a need to develop dose-controlled fertilization strategies that are plant-species specific, aim to maximize target active compounds, and consider environmental sustainability. It is emphasized that such precise fertilization approaches are strategically important not only for increasing agricultural productivity but also for ensuring the standardization and quality of pharmacologically valuable plant compounds used in medicine. Further research at the molecular level is suggested to contribute to a better understanding of the effects of fertilization on secondary metabolism.

KEY WORDS: Fertilization, Secondary metabolite, Medicinal and aromatic plants, Essential oils, Macro and micro nutrient elements, Sustainable agriculture.

INTRODUCTION

Throughout human history, medicinal and aromatic plants have played a crucial role in nutrition and healthcare [1]. The sustainable management of medicinal and aromatic plants is of great importance both nationally and internationally, considering macroeconomic structures, environmental conditions, healthcare services, employment opportunities, and the conservation of genetic resources [2].

The increasing awareness of the negative effects of chemical and synthetic substances has led to the 21st century being referred to as the "age of medicinal plants" [3]. Furthermore, the contribution of medicinal plants to biodiversity and ecological stability in agricultural ecosystems, along with the preservation of product quality and production sustainability, are also noteworthy aspects [4].

Due to the bioactive compounds they contain, medicinal and aromatic plants have gained significant importance in the pharmaceutical, cosmetic, and food industries. Plant active compounds form the basis of the pharmacological efficacy of medicinal and aromatic plants. Secondary metabolites such as alkaloids, flavonoids, terpenoids, and essential oils found in these plants are synthesized in relation to the plant's defense mechanisms. The quantity and quality of these compounds are directly influenced by the plant's genetic makeup, as well as environmental and agricultural factors [5].

In the cultivation of medicinal and aromatic plants, fertilization is one of the fundamental agricultural practices that directly affect plant development, biochemical compound content, and essential oil yield. The type and dose of applied fertilizer significantly shape the functioning of plant metabolism and the synthesis of secondary metabolites. Organic, mineral, and bio-fertilizer applications can impact quality parameters such as yield, phenolic compound levels, antioxidant capacity, and essential oil content at varying rates. Particularly, organic and biological fertilizers are reported to support sustainable agricultural production by reducing the negative environmental impacts of chemical fertilizers. In this context, determining appropriate fertilization strategies is of great importance for both improving product quality and ensuring environmental sustainability [6].

Macro (N, P, K) and micro (Fe, Zn, Mn) nutrient elements used in fertilization play fundamental roles in regulating primary and secondary metabolic processes. The application dose, timing, and method of these elements are critically important in determining the yield and quality of active compounds, especially in medicinal and aromatic plants [7]. Recent studies indicate that fertilization can have positive effects on plant active compound synthesis, but this effect may vary depending on the plant species and the type of fertilizer used [8].

Studies aimed at understanding the role of fertilization in plant active compound (secondary metabolite) synthesis are of strategic importance not only for an efficient production process but also for providing high-quality botanical raw materials for pharmaceutical purposes [9]. This review study aims to examine the effects of different fertilizer types and application doses on secondary metabolite synthesis in medicinal and aromatic plants, based on existing literature, and to provide a scientific contribution to sustainable, high-quality production goals.

Literature Review: In recent years, the regulation of active compound production in medicinal and aromatic plants through fertilization practices has become a significant focus of scientific research. Plant active compounds consist of secondary metabolites such as alkaloids, flavonoids, phenolic compounds, essential oils, and terpenoids. The synthesis of these compounds is largely related to the plant's nutritional status and environmental factors [8].

Fertilization is an agricultural input that can directly affect both primary and secondary metabolic pathways. However, in recent years, it has been more deeply scientifically understood that fertilization not only affects macro yield parameters but also directly influences the secondary metabolism of plants [10]. Secondary metabolites, such as alkaloids, flavonoids, phenolic compounds, terpenoids, and essential oils, are biochemical compounds that play a role in plant defense mechanisms and often determine the pharmacological value of medicinal and aromatic plants [11].

Numerous studies have investigated the effects of fertilization on the production of secondary metabolites, revealing that these effects vary depending on the fertilizer type, application dose, and timing [8, 32]. Therefore, in recent years, not only the effects of fertilization on growth and development but also its effects on the biosynthesis of these valuable compounds have been extensively researched [10].

The effect of fertilization on secondary metabolite production particularly depends on the presence of macro and micro nutrient elements that play a role in plant growth and metabolic processes. Macro elements like nitrogen (N), phosphorus (P), and potassium (K) play critical roles in fundamental physiological processes such as plant development, protein synthesis, energy transfer, and osmotic balance. Micro elements such as zinc (Zn), iron (Fe), and manganese (Mn) have direct effects on regulating enzymatic activities and the functionality of metabolic pathways [7, 10]. Specifically, nitrogenous fertilizer applications can increase the production of essential oils and alkaloids, while excessive nitrogen use can lead to metabolic imbalances and a decrease in secondary metabolites [12].

They reported that nitrogen fertilization positively affected the quality and quantity of essential oil in Mentha piperita. Similarly, deficiencies or excesses of elements like potassium and phosphorus can directly influence flavonoid synthesis pathways, leading to significant changes in the biochemical quality of the product. The perennial nature of Izmir oregano (Origanum onites L.) and its multiple harvests mean it removes high amounts of nutrients. [13] study emphasized in their study that nitrogenous fertilizers significantly increased yield and dry herb amount, especially from the second year onwards, and that applying fertilizer two or three times was beneficial for yield.

Furthermore, phosphorus fertilizer applications were recommended during planting and spring periods. [14] study reported that potassium fertilization improved oil quality in medicinal and aromatic plants. Micro elements, on the other hand, act as important cofactors in regulating enzymatic activities and the biosynthesis of metabolites.

Deficiencies of elements like zinc and iron can negatively affect flavonoid and phenolic compound production, whereas balanced micro-nutrition improves the metabolite profile [15, 16, 17]. However, excessive fertilization can lead to metabolic imbalances, oxidative stress, and even a decrease in active compounds. Therefore, determining optimum doses and strategies is critical for both productivity and environmental sustainability.

The use of organic fertilizers positively supports the accumulation of secondary metabolites by stimulating soil fertility and microbial activities, while also improving the biosynthesis pathways of plants [18, 19]. However, excessive fertilization can create metabolic stress and cause a reduction in active compound production. Organic fertilizers have been shown to improve soil structure, stimulate root development, and enhance the synthesis of secondary metabolites [19,15, 16, 17]. They reported that organic and inorganic fertilizers applied to Mentha piperita significantly affected essential oil composition. Therefore, the importance of organic and balanced fertilization within sustainable agricultural approaches is further increasing [20].

Organic and bio-chemical fertilizers have been shown to increase essential oil and phenolic compounds in basil, improving its antioxidant activities. These applications support product quality and environmental sustainability by reducing chemical fertilizer use [21]. One study reported in their study that chicken manure was effective in essential oil yield and that vermicompost also increased flavonoid content and antioxidant activity [22].

Bio-fertilizer use increases essential oil percentage and yield by enabling microorganisms around the roots to produce plant growth-promoting compounds [23]. Seed inoculation with microorganisms like Azotobacter has compensated for nitrogen deficiency as an alternative to chemical fertilizer use [24]. Studies on fennel and anise show that the combined use of organic and bio-fertilizers increases essential oil yield [25].

Fertilizer applications in the cultivation of medicinal and aromatic plants, especially basil, are reported to have positive effects on fresh and dry yield and essential oil content [26,27]. However, the effects of fertilizers on phenolic compounds vary depending on the application type, with phenol content differing based on the type of fertilizer used [6, 28]. According to one study, the phenol content in plants depends on the type of fertilizer applied [28].

In a study on ginger (Zingiber officinale), increased photosynthesis through soil improvement enhanced flavonoid and phenol content, thereby boosting the plant's antioxidant activity [29]. In roselle (Hibiscus sabdariffa), bio-fertilizer inoculation increased plant diameter, and seed diameter inoculated with nitroxin was 2% higher than the control group [30]. Research on goldenberry (Physalis alkekengi) found that a combination of bio-fertilizer and bio-sulfur increased the number of lateral branches. Additionally, a combination of vermicompost and nitroxin on rosemary (Rosmarinus officinalis) was reported to increase plant dry weight and essential oil percentage [31].

In recent years, using molecular biology techniques, the effects of fertilization on gene expression and enzymatic activities have begun to be investigated in more detail. These approaches facilitate the understanding of the regulatory roles of nutrient elements in metabolic pathways and provide a basis for the development of precise fertilization strategies [11,32].

The molecular-level regulation of secondary metabolites depends on explaining the complex biochemical pathways in plant metabolism through classical and molecular biology research [11]. The contributions of molecular biology techniques to understanding the effects of fertilization on gene expression and enzymatic activities allow for more precise and effective management of secondary metabolite production [32]. These techniques are used to optimize the effectiveness of fertilization by helping to understand the regulatory mechanisms in plant metabolic processes.

The literature emphasizes that integrated and controlled fertilization strategies yield more sustainable results in increasing yield and quality in medicinal and aromatic plants [7]. At the same time, these studies facilitate the understanding of the regulatory roles of nutrient elements in metabolic pathways and provide a basis for the development of precise fertilization strategies [8].

In conclusion, the effect of fertilization on the biosynthesis of secondary metabolites is of strategic importance for increasing plant production and product quality. However, to maximize this effect, fertilization practices need to be planned more precisely and integrally in line with the principles of environmental sustainability and economic efficiency. Fertilization strategies should be customized according to the plant species, targeted metabolites, and environmental conditions to increase the production of active compounds in medicinal and aromatic plants.

Effects of Macro Nutrient Elements: Macro nutrients such as nitrogen (N), phosphorus (P), and potassium (K) form the fundamental building blocks of plant metabolism. Nitrogen is involved in protein and amino acid synthesis, phosphorus in energy transfer (ATP) and DNA synthesis, and potassium in osmotic balance and enzyme activation. For instance, two study demonstrated that nitrogen and phosphorus fertilization applied to Vitex negundo significantly increased polyphenol and essential oil content [7, 8].

Nitrogen Fertilization: Nitrogen, while being an essential macro nutrient for plant growth, exhibits a dual, dose-dependent effect on secondary metabolism. Recent research indicates that fertilization regimes regulate active compound concentrations, particularly in plants with high essential oil content. Many studies have found that appropriate nitrogen application can increase menthol and essential oil synthesis, while excessive doses can negatively affect this synthesis [12]. Low-dose nitrogen application, especially in medicinal and aromatic plants, enhances essential oil synthesis [12, 19, 32]. A study on Ocimum basilicum reported that moderate nitrogen application significantly increased linalool and methyl chavicol ratios [19]. Similarly, in Mentha arvensis, levels of menthol and menthone, and in Ziziphora clinopodioides, monoterpene compounds like menthone, menthol, and pulegone, were reported to increase with nitrogen döşe [11].

One study identified 612 metabolites in a metabolomic analysis of Goji berry subjected to three different nitrogen levels, with significant changes detected in 53 of them [33]. These changes were concentrated particularly in compounds such as lipids, fatty acids, organic acids, and phenolamides. The findings reveal that nitrogen fertilization affects the quality components of Goji berry at a molecular level [34].

All these findings indicate that fertilization strategies should be carefully planned not only in terms of yield but also with regard to quality parameters. Fertilization programs optimized according to plant species, soil properties, and targeted active compounds are one of the cornerstones of sustainable agriculture.

Phosphorus and Potassium Fertilization: Phosphorus and potassium are macro nutrient elements that play significant roles in plant metabolism and particularly promote the synthesis of flavonoid and phenolic compounds. Potassium plays an important role in carbon metabolism and enzymatic reactions, supporting phenolic compound production [10]. Furthermore, the positive effects of phosphorus on plant growth and metabolism are directly related to the production of phenolic compounds and essential oil composition. A recent study on Vitex negundo observed that phosphorus fertilization increased total phenolic and flavonoid content, with significant increases in the proportion of compounds like β-caryophyllene and eremophilene in the essential oil composition [7]. Similarly, one study demonstrated that phosphorus doses altered the flavonoid profile and antioxidant capacity in Lycium barbarum (goji) fruits [35].

In medicinal and aromatic plants, phosphorus fertilization shows distinct positive effects on vegetative growth, essential oil yield, and secondary metabolite production. Studies conducted on various plants have revealed that optimum phosphorus doses vary depending on the plant species and growing conditions, but applications generally ranging between 20–250 kg/ha have improved yield and quality [36, 37, 38]. Specifically, the quantities of components such as thymol, cineole, camphor, and flavonoid derivatives significantly increased with certain phosphorus doses [39, 40].

Potassium plays a critical role in the synthesis of secondary metabolites in medicinal plants and positively influences the production of metabolites such as phenolic compounds, flavonoids, and terpenoids [41]. For example, one study showed that potassium application in basil (Ocimum basilicum) increased phenolic and flavonoid content, thereby enhancing antioxidant capacity [42]. Similarly, one study reported that potassium fertilization increased essential oil components, particularly menthol content, in peppermint (Mentha piperita) [40]. These studies support that potassium promotes secondary metabolite production in medicinal plants, improving plant quality [43].

Potassium deficiency can negatively affect enzymatic reactions involved in flavonoid synthesis, thereby reducing the plant's antioxidant capacity. This directly impacts product quality, especially in plants cultivated for food and pharmaceutical purposes.

Effects of Micro Nutrient Elements: Micro elements such as zinc (Zn), iron (Fe), manganese (Mn), and boron (B) play an important role as cofactors for enzymes involved in secondary metabolite synthesis in plants. A deficiency of these elements can lead to a decrease in the production of flavonoid and phenolic compounds. Zinc and iron are associated with the phenylalanine ammonia-lyase (PAL) enzyme, which is involved in the synthesis of flavonoids and phenolic compounds. Zinc and iron deficiencies can reduce the activity of these enzymes, negatively impacting secondary metabolite production [32].
Zinc (Zn) participates in important biophysicochemical processes in plants, such as protein synthesis, gene regulation, and as a cofactor for antioxidant enzymes.

It also helps reduce oxidative damage under abiotic stress conditions [44]. Zinc contributes to increased essential oil production and phytochemical components by protecting plants against water insufficiency and drought stress [45, 46]. Furthermore, zinc enhances nitrogen and phosphorus efficiency in plants, mitigating the negative effects of nutrient deficiencies [47].

The impact of micro element-supported fertilization programs has been confirmed, particularly in plants like Thymus vulgaris and Salvia officinalis, by improving essential oil quality. One study highlighted that fertilization with micro nutrient elements increased secondary metabolite production and essential oil quality in these plants [32].

Effects of Organic and Inorganic Fertilizers: The effects of organic and inorganic fertilizers on secondary metabolite production in plants differ significantly. While organic fertilizers can indirectly enhance secondary metabolite production by positively influencing soil microbiota, inorganic fertilizers exhibit faster and more direct effects [48]. Organic fertilizers support soil microbiota, increasing microorganism activity and thereby stimulating plant metabolic activities. One study stated that organic fertilizers enrich soil microorganisms, enhancing biological activity, which indirectly triggers secondary metabolite production [18].

It has been highlighted in many studies that organic materials such as farmyard manure, compost, and vermicompost have distinct positive effects on secondary metabolites [18, 15, 16, 17]. A study on Melissa officinalis reported that organic fertilizers significantly increased both total phenolic content and rosmarinic acid levels [49]. Furthermore, a meta-analysis by [15, 16, 17] stated that organic fertilization increased the amount of active compounds by an average of 18%, with compost and vermicompost applications being particularly effective.

Inorganic fertilizers, on the other hand, provide nutrients to plants more rapidly and are directly utilized in metabolic

activities. However, excessive use can lead to salt accumulation in the soil and disruption of microbial balance, causing long-term negative effects [8]. The correct combination of organic and inorganic fertilizers can optimize both plant growth and the quality of active compounds.

Studies demonstrate that organic fertilizers provide more sustainable and long-term effects on plants' secondary metabolism. It has been noted that organic fertilizers, especially by increasing microorganism activities, facilitate nutrient uptake by plants, resulting in increased proportions of essential oils, flavonoids, and other phenolic compounds. These findings provide an important indication that organic fertilizers improve soil health and support biodiversity.

CONCLUSION

Fertilization is a crucial agricultural practice that directly influences the production of active compounds in plants. The balanced and strategic use of macro and micro nutrient elements regulates plant metabolic processes, thereby enhancing secondary metabolite synthesis. Recent research indicates that fertilization not only increases plant biomass but also optimizes the quality and quantity of active compounds. Particularly in medicinal and aromatic plants, the impact of fertilization improves the biochemical processes of these plants, increasing the production of compounds with high pharmacological value [48].

The integrated use of organic and inorganic fertilizers ensures the sustainable support of plant growth and soil health. While organic fertilizers have long-term positive effects on active compound production by increasing soil microbial activities, inorganic fertilizers provide short-term nutrient supply to plants [8]. However, since the dosage, timing, and type of fertilizer can affect plant metabolic activities in different ways, the development of plant-specific fertilization programs is of great importance [12,34].

Future studies at the molecular level will elucidate in more detail the mechanisms of fertilization on gene expression, enzymatic activities, and metabolite accumulation. This will enable the development of more precise and effective nutrient strategies. Concurrently, using biotechnological approaches, the optimization of active compound production in medicinal plants should be targeted. Considering sustainable agriculture and environmental impacts, the combined use of organic and inorganic fertilizers stands out as the most ideal recommended approach [11].

In conclusion, the yield and quality of active compounds in medicinal and aromatic plants can be increased not only by focusing on yield enhancement but also by supporting plant metabolism in a balanced way with nutrients. In this regard, the development of plant-specific fertilization programs will be an important step from a sustainable agriculture perspective. In the future, examining the interactions between fertilization practices and plant genetics will further contribute to increasing the efficiency of plant active compound production.

Conflict of interest: None

Financial support: None

Ethhas been reported to be statement: None

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International Journal of Biomedical Research Science (IJBRS)
An Open Access International Journal
Online ISSN:_____
Vol 01 No (1) Jan-Feb-Mar-Apr 2025
https://www.ijbrs.com/

Phytochemical Insights into *Aloe vera* and *Punica granatum*: A Comprehensive Review

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ARTICLE INFO

Received Date: 15/01/2025
Accepted Date: 12/03/2025
Publication Date: 30/04/2025
Page Number:- 35-38
Available at: www.ijbrs.com

ABSTRACT:

Aloe vera and *Punica granatum* are two renowned plants celebrated for their medicinal properties and nutritional benefits. This comprehensive review aims to provide an in-depth analysis of the phytochemical constituents of these plants, highlighting their bioactive compounds, therapeutic applications, and potential health benefits. A thorough examination of existing literature reveals a diverse array of phytochemicals, including anthraquinones, flavonoids, phenolic acids, and terpenoids in *Aloe vera*, and punicalagins, ellagic acid, and anthocyanins in *Punica granatum*. These compounds have been associated with various pharmacological activities, such as antioxidant, anti-inflammatory, antimicrobial, and anticancer and antimelanogenic properties. The review discusses the current state of knowledge on the phytochemical profiles of these plants, their potential therapeutic applications, and future research directions. By exploring the phytochemical insights into *Aloe vera* and *Punica granatum*, this review aims to provide a foundation for further research and development of these plants as potential therapeutic agents. The findings of this review underscore the significance of these plants in traditional medicine and their potential to contribute to the development of novel pharmaceuticals and nutraceuticals.

KEY WORDS: *Aloe vera*; *Punica granatum*; Phytochemicals; Antimelanogenic; Pharmaceuticals.

INTRODUCTION

The great majority of people, especially those who reside in rural areas, rely heavily on herbal remedies. Numerous therapeutic plants that have been studied have scientific evidence that is well-documented. The use of plants to cure a variety of illnesses has seen a sharp increase in interest in recent years. Additionally, more research has been done on these natural compounds' potential medical and therapeutic benefits. However, only a small number of plant-based medications were able to enter clinical usage, and not even a dozen plant-based medications were accepted into the National Formulary [1, 2].

Aloe vera and *Punica granatum*, two plants with rich histories in traditional medicine, have garnered significant attention in recent years due to their diverse array of phytochemicals and potential therapeutic applications. *Aloe vera*, known for its soothing gel and skin-protecting properties, has been used for centuries to treat various ailments, from burns to digestive issues. *Punica granatum*, commonly referred to as pomegranate, has been revered for its antioxidant-rich juice and potential health benefits, ranging from cardiovascular protection to anti-cancer properties. Both plants owe their medicinal properties to a complex mixture of bioactive compounds, including phenolic acids, flavonoids, anthraquinones, and terpenoids [3, 4].

Aloe vera contains a diverse array of bioactive compounds, including anthraquinones, flavonoids, phenolic acids, and terpenoids. These phytochemicals have been associated with various pharmacological activities, such as antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. Specifically, anthraquinones of *Aloe vera*, like aloin and aloe-emodin, have shown potential in treating various health conditions. On the other hand, *Punica granatum* is abundant in punicalagins, ellagic acid, and anthocyanins, which are powerful antioxidants that may help protect against oxidative stress, inflammation, and cell damage.

The punicalagins in *Punica granatum* have been shown to have potent antioxidant and anti-inflammatory effects, while ellagic acid has demonstrated potential anticancer properties. Overall, the phytochemical constituents of *Aloe vera* and *Punica granatum* make them valuable plants for medicinal and nutritional purposes, with potential applications in pharmaceuticals, nutraceuticals, and cosmetics. Further research is needed to fully understand the therapeutic potential of these plants and their bioactive compounds [5, 6].

Nowadays, Aloe vera plant is known for its use for several purposes in dermatology [7]. Considering the availability of several clinical trials on the effect of Aloe vera on the prevention and healing of skin wounds, as well as its popularity among people and widespread use in the cosmetic industry, as research continues to uncover the phytochemical profiles of these plants, their potential uses in pharmaceuticals, nutraceuticals, and cosmetics are becoming increasingly evident. This comprehensive review aims to provide an in-depth examination of the phytochemical constituents of *Aloe vera* and *Punica granatum*, highlighting their therapeutic applications and future research directions.

Phytochemical Constituents of *Aloe vera*: *Aloe vera* contains over 200 bioactive chemicals, including phenolics, enzymes, vitamins, saccharides, and low molecular weight substances. Aloe vera is a rich source of phytochemical constituents, including anthraquinones, flavonoids, phenolic acids, and polysaccharides. Anthraquinones, such as aloin and aloe-emodin, exhibit laxative, anti-inflammatory, and antimicrobial properties [8]. Flavonoids, like kaempferol and quercetin, possess antioxidant and anti-inflammatory effects [9]. Phenolic acids, including caffeic acid and ferulic acid, contribute to *Aloe vera* 's antioxidant and antimicrobial activities [10]. Polysaccharides, particularly glucomannans and acemannan, stimulate immune responses, promote wound healing, and exhibit anti-inflammatory properties [11]. Other constituents, such as vitamins A, C, and E, and minerals like calcium and potassium, add to nutritional and therapeutic value of *Aloe vera*.

Recent studies have isolated and characterized various phytochemicals from *Aloe vera*, highlighting their potential health benefits. For example, acemannan has been shown to stimulate macrophage activation and enhance immune responses [12]. The phenolic compounds of *Aloe vera* have demonstrated antioxidant and anti-aging effects [13]. The diverse phytochemical profile of Aloe vera supports its traditional use in medicine and its modern applications in skincare, wound care, and dietary supplements.

Phytochemical Constituents of *Punica granatum* : *Punica granatum*, commonly known as pomegranate, is a rich source of diverse phytochemical constituents, including ellagitannins, anthocyanins, flavonoids, and phenolic acids. Ellagitannins, such as punicalagins and punicalins, are pomegranate's most abundant and bioactive compounds, exhibiting potent antioxidant, anti-inflammatory, and anti-cancer properties. Anthocyanins, responsible for pomegranate's vibrant red color, have been shown to possess antioxidant and anti-inflammatory effects. Flavonoids, like quercetin and kaempferol, contribute to pomegranate's cardiovascular protective effects. Phenolic acids, including ellagic acid, have demonstrated anti-cancer and anti-inflammatory activities. Other constituents, such as punicic acid, a polyunsaturated fatty acid, may also contribute to pomegranate's health benefits [14].

Therapeutic Applications: *Aloe vera* and *Punica granatum* have diverse therapeutic applications due to their bioactive compounds. Gel of *Aloe vera* is used topically for wound healing, treating skin conditions like acne, eczema, and psoriasis [8, 15, 16]. Its anti-inflammatory and antimicrobial properties reduce inflammation and prevent infections. Oral consumption of *Aloe vera* juice may help manage gastrointestinal issues like constipation and irritable bowel syndrome (IBS) [17].

Pomegranate is an ancient fruit with an illustrious medical history and has been the subject of classical reviews for over 100 years. An explosion of interest in the numerous therapeutic properties of *Punica granatum* over the last decade has led to numerous *in vitro*, animal, and clinical trials. Pomegranate is a potent antioxidant, superior to red wine and equal to or better than green tea. In addition, anticarcinogenic and anti-inflammatory properties suggest its possible use as a therapy or adjunct for prevention and treatment of several types of cancer and cardiovascular disease [14, 18, 19, 20]. Pomegranate juice may help lower blood pressure and cholesterol levels, reducing the risk of cardiovascular disease. Its antioxidant properties may also protect against neurodegenerative disorders like Alzheimer's and Parkinson's.

The combination of *Aloe vera* and *Punica granatum* may enhance therapeutic benefits. Their synergistic antioxidant and anti-inflammatory effects could provide protection against chronic diseases like diabetes, cancer, and cardiovascular disease. Wound-healing properties of *Aloe vera* may be augmented by pomegranate's antimicrobial and anti-inflammatory effects, promoting faster recovery.

Studies have demonstrated the potential of these plants in managing various health conditions. *Aloe vera* 's gel has been shown to accelerate wound healing, while pomegranate extracts have been found to inhibit cancer cell growth. Further research is needed to fully explore the therapeutic potential of *Aloe vera* and *Punica granatum.*

Pharmacological Activities: *Aloe vera* and *Punica granatum* (pomegranate) both exhibit diverse pharmacological activities. The properties of *Aloe vera* include anti-inflammatory, antimicrobial, antioxidant, and laxative effects, aiding in wound healing, skin conditions, and gastrointestinal issues [17, 21, 22]. *Punica granatum* is rich in antioxidants, showing

anti-inflammatory, antimicrobial, and anti-cancer properties. Its extracts may help protect against cardiovascular diseases, neurodegenerative disorders, and certain cancers [23, 24, 25]. Both *Aloe vera* and pomegranate have potential anti-diabetic effects, with Aloe vera possibly regulating blood sugar levels and pomegranate extracts improving insulin sensitivity. Together, they offer a range of health benefits, supporting their traditional and modern uses in medicine, skincare, and dietary supplements. Their combined antioxidant and anti-inflammatory effects may enhance overall well-being and disease prevention.

Future Research Directions: While *Aloe vera* and *Punica granatum* have been extensively studied, further research is needed to fully understand their therapeutic potential. Future research directions for *Aloe vera* and *Punica granatum* include investigating their potential therapeutic applications in various diseases, such as cancer, cardiovascular disease, and neurodegenerative disorders. Studies could focus on isolating and characterizing specific bioactive compounds, understanding their mechanisms of action, and evaluating their efficacy in clinical trials. For instance, acemannan of Aloe vera has shown promise in immunotherapy [22], while punicalagins from *Punica granatum* have demonstrated anti-cancer effects [24]. Research could also explore the synergistic effects of combining Aloe vera and *Punica granatum* extracts, potentially leading to new therapeutic approaches. Additionally, investigations into their potential anti-inflammatory, antimicrobial, and antioxidant effects could provide further insights into their health benefits. Standardization of extracts and identification of optimal dosages are also crucial areas of research.

Recent studies have laid the groundwork for these future directions. For example, research on wound-healing properties of Aloe vera and cardiovascular benefits of *Punica granatum* highlights their potential for therapeutic applications [8, 20]. Further research is necessary to fully explore the potential of these plants and translate their benefits into clinical practice.

CONCLUSION

Aloe vera and *Punica granatum* are two plants with rich histories in traditional medicine, renowned for their medicinal properties and nutritional benefits. Their phytochemical constituents, including phenolic acids, flavonoids, anthraquinones, and terpenoids, contribute to their therapeutic applications. This comprehensive review highlights the potential health benefits of *Aloe vera* and *Punica granatum,* including antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. Further research is needed to fully understand the therapeutic potential of these plants and their bioactive compounds.

ACKNOWLEDGEMENT

The authors are thankful to the Secretary and Principal of Saifia Science College, Bhopal, India, for providing the necessary facilities

Consent for publication: Not applicable.

Availability of data and material: All the data generated and analysed during the study are included in the main manuscript.

Competing interests: The authors declare that they have no competing interests.

Funding: NA

Ethics and Consent to Participate declarations: not applicable

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International Journal of Biomedical Research Science (IJBRS)

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