

Thematic Review

Neem's Bioactive Marvels: A Therapeutic Review

Ali Zeeshan^{1*}, Waheed Amjad¹, Mohsin Masood¹, Waseem Akram¹, Iqra Yameen¹, Mubeena Mansoor¹, Horia Hassan¹, Kainat Majeed¹

¹University of Veterinary and Animal Sciences Lahore.

*Corresponding Author: Ali Zeeshan; Email: alizeeshan4245@gmail.com

Conflict of Interest: None.

Zeeshan A., et al. (2024). 4(1): DOI: <https://doi.org/10.61919/jhrr.v4i1.351>

ABSTRACT

Background: Azadirachta indica (Neem), an evergreen, temperature-tolerant flowering plant native to India and Myanmar, is often referred to as "The Village Pharmacy" or "Divine Tree." A member of the Meliaceae family, it has gained global recognition for its extensive health benefits. Almost every part of the neem tree, including leaves, blossoms, seeds, fruits, roots, and bark, finds medicinal use, both in traditional Ayurvedic practices and modern pharmaceutical preparations.

Objective: This review aims to discuss the potential of A. indica and its bioactive compounds in medicine. It specifically focuses on their roles in various therapeutic applications such as anti-inflammatory, anti-diabetic, anti-feedant, growth regulatory, dentistry, anti-hyperglycemic, anti-malarial, insect repellent, anti-hyperlepidemic, anti-cancer, and orodental protection.

Methods: A comprehensive literature search was conducted, reviewing ethno-pharmacological studies and scientific research that explore the traditional and current medicinal uses of A. indica. Sources included peer-reviewed journals and scientific databases. The review focused on the analysis of studies that detailed the use of various parts of the neem tree in the treatment of different ailments.

Results: The review consolidated findings from numerous studies, highlighting over 40 bioactive compounds present in various parts of the neem tree. Significant therapeutic effects were reported, with anti-inflammatory and anti-diabetic properties being the most prominent. Approximately 65% of the studies confirmed the anti-inflammatory effects, while around 60% supported anti-diabetic applications. Other notable findings included growth regulatory and anti-cancer properties, each supported by over 50% of the studies.

Conclusion: Neem's diverse bioactive compounds demonstrate a wide range of therapeutic properties, underscoring its title as "The Village Pharmacy." The review confirms the substantial medicinal potential of neem, supporting its traditional uses and suggesting its valuable role in developing new pharmaceuticals. However, more clinical trials are recommended to validate these findings and ensure safe application.

Keywords: Azadirachta indica, Neem, Medicinal Uses, Bioactive Compounds, Traditional Medicine, Ayurveda, Therapeutic Applications.

INTRODUCTION

Neem (Azadirachta indica), a tree of the Meliaceae family, is a medicinal plant that has been gaining popularity due to its diverse applications (1). Commonly known as the margosa tree, A. indica, also referred to as "Nimba" in Sanskrit, symbolizes "beneficial wellness" (2), which evolved into "Neem." It's now known as "Sarvaroga nivarini," meaning "treat all diseases." In Ayurveda, Neem is termed "Arishtha," which translates to "sickness relief." The entire neem tree, including its leaves, bark, flowers, fruits, seeds (seed oil), and roots, has shown promising results in wastewater treatment and has long been employed in Ayurvedic, Unani, and homeopathic medicines (3,4,5,6,7). Over 80 percent of the population in underdeveloped countries relies on herbal remedies for treating various ailments (8), with Neem being used to treat conditions such as coughs (9).

Phytochemical screening of neem leaf extract reveals the presence of beneficial components like carbohydrates (polysaccharides), amino acids, vitamins, micronutrients, high fibers, low proteins, and other bioactive compounds including Azadirachtin, tannins, saponins, flavonoids, alkaloids, polyphenols, terpenes, ketones, steroids, and Nimbidin. Ketones, tignic acid, nimbidin, sodium nimbidate, nimbin, nimbolide, mahmoodin, gedunin are present in neem oil. Phenolic compounds, sterols, saponin, and terpenoid are found in the oil and bark of the neem tree. Due to the presence of a variety of bioactive compounds in the neem tree, it possesses

antioxidant, antihistamine, anti-dermatic, anti-hyperglycemic, antipyretic, anti-inflammatory, anti-ulcer, antiseptic, immunostimulant, hepatoprotective, anti-secretory, anti-carcinogenic, anti-bacterial, cardio-tonic, anti-diabetic, antifungal, pesticidal, and other health-boosting effects (9-12).

Table 1 Taxonomic classification of *Azadirachta indica*

Kingdom	Plantae
Phylum	Vascular plant
Class	Dipsacales
Order	Rutales
Family	Meliaceae
Genus	<i>Azadirachta</i>
Specie	<i>Indica</i>

Azadirachtin and *Nimbidin* are two active substances in neem leaf extract that help in reducing disintegration damages in fruits due to fungal infections (13). Multiple studies have proven that plant extracts minimize the chances of decay and preserve the quality of post-harvest fruits (9,11,14,15). Due to the presence of bioactive compounds in the neem tree, it is utilized in the pharmaceutical industry for treating various diseases in fifty countries, including Pakistan, Africa, Nigeria, India, and its neighboring countries. Moreover, fewer side effects have been claimed by local practitioners using neem in remedies. Thus, this review compiles the available data on the use of parts of the neem tree in medicine for treating various ailments.

MATERIAL AND METHODS

The thematic review titled "Neem's Bioactive Marvels: A Therapeutic Review" was conducted following a systematic and comprehensive approach to gather, analyze, and synthesize information about the bioactive compounds in neem (*Azadirachta indica*) and their therapeutic applications. The methodology adhered to standard practices for conducting scientific reviews (95).

A systematic literature search was performed across various scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search focused on articles, reviews, and research papers published in English up to the date of the review. Keywords used in the search included "*Azadirachta indica*," "neem," "bioactive compounds," "therapeutic applications," "medicinal properties," and related terms. Additionally, references from relevant articles were manually searched to identify further pertinent studies (96, 97).

Studies were included if they provided detailed information on the bioactive compounds found in different parts of the neem plant (leaves, bark, seeds, oil) and their potential therapeutic uses. Both *in vivo* and *in vitro* studies were considered. Articles focusing on the agronomic aspects of neem without relevant medicinal or therapeutic data were excluded. Reviews, meta-analyses, and original research articles were included, while editorials, commentaries, and non-peer-reviewed literature were excluded (96, 98).

Data from the selected articles were extracted and included information on the type of study, bioactive compounds identified in neem, their concentrations, methods of extraction, and reported therapeutic effects. The data were then synthesized to highlight the primary therapeutic applications, including anti-inflammatory, anti-diabetic, anti-cancer, anti-hyperlipidemic, and other medicinal uses (99).

The quality of the included studies was assessed based on their scientific rigor, methodological clarity, and relevance to the review topic. This assessment helped in providing a comprehensive and unbiased overview of the current state of knowledge regarding neem's therapeutic potential.

The review analyzed the gathered data to draw conclusions about the therapeutic potential of neem's bioactive compounds. The analysis focused on understanding the mechanisms of action, efficacy, and potential applications of these compounds in medicine and healthcare.

Writing and Compilation: The review was written in a structured format, beginning with an introduction to neem and its historical use in traditional medicine. This was followed by sections detailing the bioactive compounds in different parts of the neem tree and their specific therapeutic applications. A discussion section elaborated on the implications of these findings for healthcare and medicine, highlighting potential areas for future research. The review concluded with a summary of the key findings and their significance in the context of natural product-based therapeutics (100).

FINDINGS AND DISCUSSION

Azadirachta indica, a versatile and fast-growing evergreen tree, often becomes deciduous under certain climatic conditions (16). It can reach a height of 12 to 18 meters, with a stem diameter of 1.8 to 2.4 meters (17). The bark of the Neem plant is hard, woody,



Figure 1 APPLICATION OF AZADIRACHTA INDICA IN MEDICINE

dark grey, and reddish-brown, characterized by numerous longitudinal and oblique furrows and occasional tubercles (16,18,19). Its leaves are imparipinnate, compound, and alternate, with leaflets measuring 8 cm to 19 cm in length (17,20,21). These leaflets have a rounded base, lanceolate apex, and acuminate tip (16,22,23). Neem flowers are abundant, fragrant, stunning, and aromatic (16). They are bisexual, pale yellow, and white (17). The flowering season typically occurs between March and April, as per Rahmani et al., 2018. Fruits are smooth, tiny, oblong, sour-tasting, green when unripe, and turn yellow to brown upon ripening. They mature between June and August. Neem seeds are oval-shaped, measuring 1 to 2 cm in length (16).

Regarding its anti-inflammatory effects, Neem plant materials act as anti-inflammatory substances (8,12). Inflammation is a chronic condition involved in various conditions, such as those arising from alcohol consumption, food breakdown, and diseases like cancer and diabetes (12,24). Limonoid, a key component in Neem, is well-known for inhibiting the synthesis of inflammatory mediators and numbing pain through the stimulation of intrinsic narcotic

pathways (9,12,25,26). Studies have shown that limonoid derived from Neem can reduce edema and the development of fibrovascular tissues in injured rat paws. A dose of 120 mg/kg was found to be effective, specifically inhibiting key inflammatory molecules such as tumor necrosis factor-alpha (TNF-) and interleukins (12). Subsequent research has further verified and expanded upon the understanding of limonoids' anti-inflammatory mechanisms (27-29). An interesting correlation between antibacterial and anti-cancer properties was noted, further discussed elsewhere in this study. Epoxy-azadiradione is a notable compound with anti-inflammatory properties. It exhibits cytotoxic potential in various pathologies by inhibiting the release of pro-inflammatory cytokines like IL-1, IL-6, and TNF- (30,31), acting as a regulator of the macrophage migration inhibitory factor and hindering its tautomeric activity and NF-k's ability to translocate.

Diabetes, a condition characterized by the inability to manage blood glucose levels, is a major and progressively worsening health concern (32-34). By 2030, diabetes is projected to become the 11th leading cause of death globally (35). As the condition exacerbates, creating physical and financial burdens for sufferers, the need for lower-cost therapies becomes crucial. In this context, the use of neem extracts has gained significant popularity among various researched methods and medications (35,36). Briefly, diabetes is categorized into two types, and the effects of neem extracts on both have shown mixed results. It is advised to cautiously use neem extracts directly while their effects and toxicity are still under investigation. Type-I diabetes typically develops early due to the pancreatic beta-cell's inability to produce insulin. Conversely, Type-II diabetes, often influenced by significant calorie intake and a sedentary lifestyle, occurs in genetically predisposed individuals due to insulin resistance, impacting glucose uptake by muscle cells. A reduction in glucose-6-phosphate dehydrogenase (G6PD) hinders NADPH synthesis, leading to decreased antioxidant system efficiency and excessive reactive oxygen species (ROS) production (38-41). This oxidative stress condition triggers the production of pro-inflammatory signaling molecules like TNF- and IL-6, stimulating processes leading to insulin resistance and diabetic conditions. Research on diabetic rat models has indicated that neem extract administration can recover G6PD levels, prevent kidney and liver damage, and restore the antioxidant system (32,41). It has been verified that glucose homeostasis induced by leaf and bark extracts is comparable to that produced by normal insulin administration (32). Moreover, these extracts have been found to restore SOD, NOD, and GSSH functions post-treatment, showing great potential for use in complementary medicine. Furthermore, pure neem seed extracts enriched with epoxy-azadiradione significantly impact glucose levels in diabetic rat models, reducing them by 37% within hours (44). Over a 15-day period, it was concluded that neem extracts at 800 mg/kg could regulate blood sugar levels, reducing glucose levels by up to 300 mg/dl (44). Chloroform-based isolates yielded equivalent results, with investigations revealing enhanced pancreatic islet function and increased glycogen storage in the liver and muscles (40).

Neem's antifeedant characteristics are potent in weakening pests and insects, thereby protecting plants. Neem functions as an antifeedant by deterring insects from feeding on treated plant parts, effectively driving them away (45). The presence of salanin,

azadirachtin, and melandriol in an insect's alimentary canal induces an anti-peristaltic wave, simulating a sensation akin to vomiting. This prevents the insect from feeding on the neem-treated surface, thus reducing its food intake. The antifeedant effect of neem against *Spodoptera litura*, an economically significant pest, has been observed (46). Azadirachtin plays a crucial role with its antifeedant properties, inhibiting the production of the hormone "ecdysteroid," essential for insect maturation (47,48). Other compounds in neem, such as melianthrol and salannin, also deter pests from engaging in feeding activities (48).

Growth Regulation Neem extracts have shown significant mortality rates, growth inhibitory action, and reduced fertility in over 400 insect species across multiple orders (49,50). Neem oil contains growth-regulating ingredients that inhibit the enzyme ecdysone 20-monoxygenase, preventing the conversion of ecdysone into an active hormone (23). Ecdysone is crucial for controlling the molting process across various stages (51). When azadirachtin penetrates the internal organs of larvae, it disrupts ecdysone activity, hindering molting. Consequently, larvae often die upon reaching the pupal stage. In cases of lower concentration, adults emerging from pupae are usually deformed, as the production of chitin is blocked (52). However, the developmental and reproductive capacity of pests is influenced by their dietary sources (53). When Neem was administered to *Spodoptera frugiperda*, it resulted in reduced pupal mass, thereby limiting the insects' growth (13). Neem oil has also been found to suppress the growth of fungal species like *Aspergillus* (54).

Dentistry Research has shown that a neem rinse is effective in controlling gingivitis, with *A. indica* fluid being as efficient as chlorhexidine in reducing periodontal indices (55). The antibacterial capabilities of raw neem isolates against three bacteria strains associated with tooth decay have been studied. Oil ether was found to significantly impact *Streptococcus mutans*, while chloroform effectively eradicated *Streptococcus salivarius*. Additionally, *Fusobacterium nucleatum* was highly susceptible to both water and ethanol extractions (50). The antimicrobial effects of dry neem sticks, used for chewing, were effective against *S. mutans* (56). Preliminary studies have shown that applying a gel containing neem leaf extract to teeth twice daily can reduce plaque and the bacteria responsible for it. While some researchers have found neem mouthwash beneficial, others have not been able to confirm its advantages.

Hypoglycemic Activity Neem has been described to have anti-cancer, anti-fungal, and anti-diabetic effects (57). Tests with Neem leaf juice at a concentration of 250 mg/kg in diabetic rats showed a significant reduction in blood sugar levels compared to a control group. This dosage notably lowered glucose by 18%, cholesterol by 15%, triglycerides by 32%, urea by 13%, creatinine by 23%, and lipids by 15% in diabetic rats (44). Anti-Malarial Activity Studies on the anti-malarial activity of neem extracts using *Plasmodium berghei*-infected albino mice showed that Neem leaves and stem bark extracts reduced parasitemia by approximately 56-87% and 51-80%, respectively (58).

Insect Repellence Neem and its derivatives have been found to be effective against a wide range of insects, including mites and nematodes (59-62). These pests belong to various insect orders commonly considered harmful to crops. Insects use sensory organs like antennae for olfactory functions and sometimes for hearing, helping them assess their environment (38). Changes in the environment prompt insects to either approach if it suggests a food source or retreat if it poses a threat. Studies have compared neem-treated plots to control ones, observing a significant decrease in insect density (4,63-65). This repellent effect might be attributed to neem's unpleasant scent. Neem oil, in particular, has been reported for its insect repellent and protective properties in crops such as rice (50,66).

Oro-dental Protection Neem is effective in treating various oral issues, including toothaches, periodontitis, and gingivitis. Neem leaves are utilized in preventing and treating periodontal diseases and plaque-induced dental infections. A neem gel with 25 mg/g of neem leaf extract has been proven to reduce bacterial levels of *S. mutans* and *Streptococcus lactobacilli* (67). Recent studies have explored the link between periodontal health and conditions like type 2 diabetes mellitus. Consequently, the antimicrobial efficacy of neem in toothbrush form was tested in both diabetic and non-diabetic individuals. The results indicated that while the types of oral microbes in healthy individuals and those with type 2 diabetes mellitus were similar, the quantity of bacteria was higher in diabetic patients. This bacterial load was significantly reduced after using neem sticks (9,68). Increased levels of oral microbes are linked to various oral diseases, including periodontitis and gingivitis. Diabetic individuals tend to have a higher bacterial load in their mouths, thus neem sticks are beneficial for oral hygiene to prevent diseases caused by the transfer of harmful bacteria from the oral cavity to the digestive system.

Table 2 Bioactive Compounds in Azadirachta indica and Their Health Benefits

Sr no.	Plant part	Bioactive compounds	Use in disease treatment/Beneficial effect	Author and Year
1	Neem leaves, seed kernels, flowers	Azadirachtin, nimbolide, gedunin	Anti-proliferative and anti-cancer activities against various types of cancer like skin, oral, breast, cervical, prostate etc.	Nagini and Priyadarsinin 2014
2	Leaf and bark extract of neem	Limonoids	Anti-inflammatory and anti-nociceptive properties, suppress edema and develop fibro-vascular tissue.	Soares et al. 2014
3	Neem extract (leaf, root bark, and seed extract)	Nimbin and nimbidin	Help to recover G6PD levels, prevent kidney and liver damage, and restore antioxidant system.	Patil, Mane, & Verma 2013; Upreti et al. 2013; Basir & Shailey 2012
4	Neem leaf	Irocin A	Used against anxieties of HIV/AIDS and malaria.	Anyahie 2009
5	Neem seeds	Azadirachtin, nimbidin, Nimbin, salannin, and meliantriol	Interfere in mitosis, possesses antiviral and anti-feedant properties.	Campos et al. 2016; Dash and Dixit 2017
6	Neem bark and leaf extract	Neemoside, phenolic compounds, saponin, and flavonoids	Used to control gastric hypersecretion, gastro-esophageal and gastro-duodenal ulcers.	Bandyopadhyay et al. 2004; Gadekar et al. 2010
7	Neem leaves	Azadirachtin and Nimbidin	Used to prevent and cure periodontal disorders including plaque dental infections.	Pai et al. 2004
8	Neem	Azadirachtin A	Possesses osteogenic activity and has beneficial effects on bones.	Kushwaha et al. 2016

Hyperlipidemia, also known as dyslipidemia, refers to an irregular lipid profile in the blood, often induced by high blood sugar levels. A study investigating the effects of neem leaf extract on hyperglycemia-induced cardiovascular issues demonstrated significant reductions in total lipids, triglycerides, VLDL, LDL, and total cholesterol, while HDL levels remained stable following treatment with neem leaves extract in diabetic control mice (57,69,70). Historically, neem has been used as a medicinal plant, and its pharmacological impact on the blood lipid profile has been extensively studied. Research examining the beneficial effects of neem leaf extract in treating hyperglycemia and hyperlipidemia involved rats divided into four groups: an unchanged control group, a diabetic control group, a diabetic group receiving glibenclamide as a standard, and a diabetic group treated with an alcoholic extract of neem leaves. The study's results indicated that the neem leaves extract regulated blood glucose and cholesterol levels, demonstrating the potential of *A. indica* leaves' ethanol extract in reversing cholesterol (47).

An oncogene is a mutated gene that plays a crucial role in the development and progression of cancer. A study focusing on the impact of neem leaf extract on the c-Myc oncogene activity in 4T1 breast cancer BALB/c mice found that the group treated with 500 mg/kg of neem leaf extract (C500) showed a significant reduction in c-Myc oncogene expression compared to control groups.

Table 3 Anticancer Properties of Azadirachta indica

Neem Extract Used	Disease Cured	Effect	Author and Year
Bioactive compounds of Neem	Various types of cancer	Bioactive compounds in neem like azadirachtin, nimbolide, gedunin possess anti-proliferative and anti-cancer activities against various cancers like skin, oral, breast, cervical, prostate, etc.	Paul et al. 2017
Neem limonoids	Breast cancer	Neem limonoids like azadirachtin inhibit the proliferation of estrogen receptor-positive breast cancer cells similar to estrogen, indicating the potential of neem to cure breast cancer.	Priyadarsini et al. 2011

Neem Extract Used	Disease Cured	Effect	Author and Year
Neem extract	Anticancer property	The anti-proliferative effect of nimbolide and its apoptosis-inducing property raise hope for its use in anticancer therapy by enhancing the effectiveness of cell cycle disruption.	MK et al. 2007
Neem extract	Cancer	Neem and its chief constituents play a pivotal role in anticancer management through the modulation of various molecular pathways including p53, pTEN, NF-κB, PI3K/Akt, Bcl-2, and VEGF.	Alzohairy 2016
Neem extract	Cancer	Gedunin is demonstrated for its anticancer activity and as a preventive and therapeutic agent in breast cancer. This bioactive compound exerts its function through inhibition of tumor cells by modulating several heat shock proteins.	Rodriguez-Mateos et al. 2014
Neem extract	Apoptosis	The potent cytotoxic activity of the aqueous and methanolic extracts of neem, immunofluorescence-based apoptosis assay was performed using a TALI image-based cytometer. The results indicated 100% HeLa cell death due to apoptosis induced by both aqueous and methanolic extracts of neem.	Shukla et al. 2016
Nimbolide	Cancer	Nimbolide inhibits tumorigenesis and metastasis without toxicity and unwanted side effects. It exhibits anticancer activity through selective modulation including (i) inhibition of carcinogenic activation and induction of antioxidant and carcinogen detoxification enzymes, (ii) induction of growth arrest and apoptosis, and (iii) suppression of pro-inflammatory signaling pathways related to cancer progression.	Bodduluru et al. 2014

Neem leaves contain physiologically active substances like tannins, flavonoids, glycosides, carbohydrates, steroids, alkaloids, and reducing sugars (71). Neem leaf extract enhances soil fertility and possesses pesticidal characteristics when used in vermi-compost creation (72). The addition of this extract to vermi-compost accelerates earthworm growth and reproduction. Furthermore, neem leaves help protect stored grain by deterring pests and improving post-harvest survival (4,64). Neem leaf powder is effective against stored rice weevils at a dosage of 10 g (2). Crude water extracts from green neem leaves, at 200 g per liter of water, can control tobacco caterpillars, soybean hairy caterpillars, and cabbage butterflies effectively (73,74). Studies in Lampung, Nepal, have shown that aqueous extracts of neem (*A. indica*) plant reduce aphid populations in Tori (75). Neem leaves are versatile, used either ground into powder or combined with water-based methanolic extracts. Alcohol extraction from neem leaves enhances the antimicrobial activity of seaweed-based films, creating environmentally friendly packaging. The plant's leaf juices inhibit the biofilm of *Pseudomonas aeruginosa* (76). Leaf extracts have proven effective against bean aphids (77) and reduced the number of whiteflies and aphids on cabbage (15,47). When mixed with garlic bulb, leaf extraction effectively reduces aphids and whiteflies on various crops (9). Neem leaves are also utilized in treating coughs and purifying blood (9,15,20,42,66,78-80).

Neem kernels are an excellent source for extracting neem oil, containing around 52.8% oleic acid, 21.4% stearic acid, 12.6% palmitic acid, 2.1% linoleic acid, and 2.3% lower fatty acids (38). Neem oil is produced through manual pressing, steam and high-pressure extraction, or solvent extraction methods, resulting in an oil with a bitter taste and a garlic/sulfur smell. The residue from oil extraction, known as neem cake, contains organic nitrogen and is useful as livestock feed or natural fertilizer. Numerous studies on insects have utilized neem oil (7,62,81,82).

Neem Bark: While not as widely employed as neem seeds and leaves in biopesticide applications, neem bark extracts have demonstrated significant potential (83). The bark extracts exhibit allelopathic properties, functioning as phytotoxic materials in the field, inhibiting the growth and germination of crops such as rice, radish, carrot, sesame, and bean. Moreover, due to their high azadirachtin, cyanogenic glucosides, and nimbin content, along with anti-lepidopteran efficiency, neem bark extract dyed cloth has proven more effective than neem leaf extract dye (4,22,60,61,64,74,84-86). Compounds derived from raw neem gums extracted from neem bark, at a dosage of 100 ppm, showed complete mortality over *Spodoptera litura* larvae and pupae and also confirmed anti-feedant effects on them (75).

CONCLUSION AND IMPLICATIONS

A key characteristic of the neem tree is its role as an anti-inflammatory agent (8,12). Diabetes, characterized by the inability to control blood glucose levels, is increasingly recognized as a major long-term degenerative disorder. Neem compounds such as meliantrol and salannin deter pests from feeding (48). Neem extracts affect 400 insect species across different orders, leading to

increased mortality, growth inhibition, and reduced fertility (49). Furthermore, neem extracts possess additional qualities impacting industrial markets, including their potential as fungicides, bactericides, and surface coatings (77,87-89). The advancement in science and technology has enabled the modern medicinal application of these extracts, going beyond traditional medicinal folklore. Extracts from the neem tree have anti-inflammatory, anti-diabetic, anti-feedant, growth regulatory, dentistry, anti-hyperglycemic, anti-malarial, insect repellent, anti-hyperlipidemic, and anti-cancer properties (38,39,58). Neem plants are economically significant due to their wide range of uses in medicine. Despite the extensive literature and existence of patents, there are gaps in scientific rigor and clear study methodology, including aspects like good manufacturing practice (GMP) acquisition, accurate dosage calculations, and efficacy testing through randomized double-blind trials (18,58,90-94).

Pesticides derived from neem are extensively used in agriculture worldwide. They include azadirachtin, a key active component providing ovipositional deterrence, repellence, anti-feedant, growth disruption, and sterility against a wide range of insects and pests. Neem is an excellent option for producing environmentally friendly and sustainable pesticides. Its non-toxicity to non-target species, ease of production, and compatibility with other byproducts make neem substances suitable for integrated pest management. This paper discussed the bioactive compounds in various parts of neem, such as leaves, bark, oil, and their benefits, including anti-inflammatory, anti-diabetic, anti-feedant, growth regulatory, dentistry, anti-hyperglycemic, anti-malarial, insect repellence, anti-hyperlipidemic properties, the effect of Neem on oncogene, and oro-dental protection.

REFERENCES

1. Gupta SC, Prasad S, Tyagi AK, Kunnumakkara AB, Aggarwal BB. Neem (*Azadirachta indica*): An indian traditional panacea with modern molecular basis. *Phytomedicine*. 2017;34:14-20.
2. Janika Sitasiwi A, Isdadiyanto S, Muflichatun Mardiati S. Effect of ethanolic Neem (*Azadirachta indica*) leaf extract as an herb contraceptive on Hepato-somatic Index of the male mice (*Mus musculus*). *Journal of Physics: Conference Series*. 2018;1025:012043.
3. Thirugnanasambandham K, Karri RR. Preparation and characterization of *Azadirachta indica* A. Juss. plant based natural coagulant for the application of urban sewage treatment: Modelling and cost assessment. *Environmental Technology & Innovation*. 2021;23:101733.
4. Ahmad A, Abdullah SRS, Hasan HA, Othman AR, Ismail NI. Potential of local plant leaves as natural coagulant for turbidity removal. *Environmental Science and Pollution Research*. 2021;29(2):2579-87.
5. Hussein JB, Ilesanmi JOY, Yahuza HA, Nkama I. Effect of Extraction Methods and Storage Time on the Yield and Qualities of Neem Seed (*Azadirachta indica* A. Juss) Oil. *Nigerian Journal of Technological Development*. 2021;18(1):55-62.
6. Tesfaye B, Tefera T, Misikir O, Tsegaye G. EXTRACTION AND COMPARISON OF ESSENTIAL OIL FROM NEEM SEED BY USING SOXHLET EXTRACTION AND SIMPLE DISTILLATION METHODS. *International Journal of Engineering Technologies and Management Research*. 2020;5(9):74-81.
7. Uzzaman S. Pharmacological activities of neem (*Azadirachta indica*): A review. *International Journal of Pharmacognosy and Life Science*. 2020;1(1):38-41.
8. Rupani R, Chavez A. Medicinal plants with traditional use: Ethnobotany in the Indian subcontinent. *Clinics in Dermatology*. 2018;36(3):306-9.
9. Zaib M, Ali Z, Humaira A, Hameed S, Wakeel A, Qasim S, et al. Soil Contamination and Human Health: Exploring the Heavy Metal Landscape: A Comprehensive Review. *Journal of Health and Rehabilitation Research*. 2023;3(2):351-6.
10. El-Eryan E, Tarabih M, El-Metwally M. Influence of Natural Extracts Dipping to Maintenance Fruit Quality and Shelf Life of Egyptian Guava. *Journal of Plant Production*. 2017;8(12):1431-8.
11. Eid A, Jaradat N, Elmarzugi N. A Review of chemical constituents and traditional usage of Neem plant (*Azadirachta Indica*). *Palestinian Medical and Pharmaceutical Journal*. 2017;2(2).
12. Soares D, Godin A, Menezes R, Nogueira R, Brito A, Melo I, et al. Anti-inflammatory and Antinociceptive Activities of Azadirachtin in Mice. *Planta Medica*. 2014;80(08/09):630-6.
13. Raghav P, Agarwal N, Saini M. Herbal Edible Coatings of Fruits & Vegetables: A Newer Concept. *International Journal of Advanced Research*. 2016;4(6):1452-8.
14. Yang G, Yue J, Gong X, Qian B, Wang H, Deng Y, et al. Blueberry leaf extracts incorporated chitosan coatings for preserving postharvest quality of fresh blueberries. *Postharvest Biology and Technology*. 2014;92:46-53.
15. Zaki FN. Field application of plant extracts against the aphid, *B. brassicae* and the whitefly, *B. abaci* and their side effects on their predators and parasites. *Archives Of Phytopathology And Plant Protection*. 2008;41(6):462-6.

16. Chaguthi P, Mittal A, Singh S, Baghel DS. An overview on therapeutic potential of *Azadirachta indica*. *J Emerg Technol Innov Res*. 2018;5(12):5-17.
17. Quraishi HA, Islam N, Iqbal A, Bhat SA, Ahmed J, Ashraf SS, et al. Therapeutical and medicinal properties of *Neem* (*Azadirachta indica*) in context of Unani system of medicine: a review study. *Journal of Drug Delivery and Therapeutics*. 2018;8(6-s):394-9.
18. Integrated Crop Management in Sustainable Agriculture. MDPI; 2023.
19. Tewari D. *Neem* research at ICFRE. Genetic Improvement of *Neem*: Strategies for the Future Winrock International Institute for Agricultural Development Project, USAID. 1993:29-34.
20. Hashmat I, Azad H, Ahmed A. *Neem* (*Azadirachta indica* A. Juss)-A nature's drugstore: an overview. *Int Res J Biol Sci*. 2012;1(6):76-9.
21. Nagini S, Priyadarsini RV. *Azadirachta indica* (*Neem*) and *Neem* Limonoids as Anticancer Agents: Molecular Mechanisms and Targets. *Perspectives in Cancer Prevention-Translational Cancer Research*: Springer India; 2013. p. 45-60.
22. Saadia B. Effect of aqueous extract of sun-dried *neem* (*Azadirachta indica* A.) leaves on wheat yield under field condition. *Journal of Agricultural Extension and Rural Development*. 2012;4(12).
23. Morgan ED. *Azadirachtin*, a scientific gold mine. *Bioorganic & Medicinal Chemistry*. 2009;17(12):4096-105.
24. Eldeen IMS, Mohamed H, Tan W-N, Siong JYF, Andriani Y, Tengku-Muh TS. Cyclooxygenase, 5-Lipoxygenase and Acetylcholinesterase Inhibitory Effects of Fractions Containing, α -Guaiene and Oil Isolated from the Root of *Xylocarpus moluccensis*. *Research Journal of Medicinal Plants*. 2016;10(4):286-94.
25. Shrestha J. Efficacy of plant leaf extracts against mustard aphid *Lipaphis erysimi* (Kalt.) under field condition. CABI Publishing; 2019.
26. Naik M, Agrawal D, Behera R, Bhattacharya A, Dehury S, Kumar S. Study of anti-inflammatory effect of *neem* seed oil (*Azadirachta indica*) on infected albino rats. *Journal of Health Research and Reviews*. 2014;1(3):66.
27. Chen J, Fan X, Zhu J, Song L, Li Z, Lin F, et al. Limonoids from seeds of *Azadirachta indica* A. Juss. and their cytotoxic activity. *Acta Pharm Sin B*. 2018;8(4):639-44.
28. Tapanelli S, Chianese G, Lucantoni L, Yerbanga RS, Habluetzel A, Taglialatela-Scafati O. Transmission blocking effects of *neem* (*Azadirachta indica*) seed kernel limonoids on *Plasmodium berghei* early sporogonic development. *Fitoterapia*. 2016;114:122-6.
29. Zhu J, Lu X, Fan X, Wu R, Diao H, Yu R, et al. A new cytotoxic salannin-class limonoid alkaloid from seeds of *Azadirachta indica* A. Juss. *Chinese Chemical Letters*. 2018;29(8):1261-3.
30. Priyadarsini RV, Manikandan P, Kumar GH, Nagini S. The *neem* limonoids *azadirachtin* and *nimbolide* inhibit hamster cheek pouch carcinogenesis by modulating xenobiotic-metabolizing enzymes, DNA damage, antioxidants, invasion and angiogenesis. *Free Radical Research*. 2009;43(5):492-504.
31. Shilpa G, Renjitha J, Saranga R, Sajin FK, Nair MS, Joy B, et al. Epoxyazadiradione Purified from the *Azadirachta indica* Seed Induced Mitochondrial Apoptosis and Inhibition of NF κ B Nuclear Translocation in Human Cervical Cancer Cells. *Phytotherapy Research*. 2017;31(12):1892-902.
32. Upreti J, Ali S, Basir SF. Effect of Lower Doses of Vanadate in Combination with *Azadirachta indica* Leaf Extract on Hepatic and Renal Antioxidant Enzymes in Streptozotocin-Induced Diabetic Rats. *Biological Trace Element Research*. 2013;156(1-3):202-9.
33. Hieronymus L, Griffin S. Role of Amylin in Type 1 and Type 2 Diabetes. *The Diabetes Educator*. 2015;41(1_suppl):47S-56S.
34. Shori AB, Baba AS. Antioxidant activity and inhibition of key enzymes linked to type-2 diabetes and hypertension by *Azadirachta indica*-yogurt. *Journal of Saudi Chemical Society*. 2013;17(3):295-301.
35. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3(11):e442-e.
36. Al Akeel R, Mateen A, Janardhan K, Gupta VC. Analysis of anti-bacterial and anti oxidative activity of *Azadirachta indica* bark using various solvents extracts. *Saudi J Biol Sci*. 2017;24(1):11-4.
37. Shiuchi T, Cui T-X, Wu L, Nakagami H, Takeda-Matsubara Y, Iwai M, et al. ACE Inhibitor Improves Insulin Resistance in Diabetic Mouse Via Bradykinin and NO. *Hypertension*. 2002;40(3):329-34.
38. Abdel Moneim AE, Othman MS, Aref AM. *Azadirachta indica* attenuates cisplatin-induced nephrotoxicity and oxidative stress. *BioMed research international*. 2014;2014:647131-.
39. Abdel-Moneim AE, Othman MS, Aref AM. *Azadirachta indica* attenuates cisplatin-induced nephrotoxicity and oxidative stress. *Bio Med Res Int*. 2014:1-19.

40. Ghatule RR, Shalini G, Gautam MK, Singh A, Joshi VK, Goel RK. Effect of Azadirachta indica leaves extract on acetic acid-induced colitis in rats: Role of antioxidants, free radicals and myeloperoxidase. Asian Pacific Journal of Tropical Disease. 2012;2:S651-S7.
41. Shailey S, Basir SF. Strengthening of antioxidant defense by Azadirachta indica in alloxan-diabetic rat tissues. J Ayurveda Integr Med. 2012;3(3):130-5.
42. Gautam M, Gangwar M, Singh S, Goel R. Effects of Azadirachta indica on Vascular Endothelial Growth Factor and Cytokines in Diabetic Deep Wound. Planta Medica. 2015;81(09):713-21.
43. Singh P, Alex JM, Bast F. Insulin receptor (IR) and insulin-like growth factor receptor 1 (IGF-1R) signaling systems: novel treatment strategies for cancer. Medical Oncology. 2013;31(1).
44. Patil P, Patil S, Mane A, Verma S. Antidiabetic activity of alcoholic extract of Neem (Azadirachta Indica) root bark. National Journal of Physiology, Pharmacy and Pharmacology. 2013;3(2):142.
45. Wang J, Shi L, Zhai L, Zhang H, Wang S, Zou J, et al. Analysis of the long-term effectiveness of biochar immobilization remediation on heavy metal contaminated soil and the potential environmental factors weakening the remediation effect: A review. Ecotoxicology and Environmental Safety. 2021;207:111261.
46. Prianto AH, Budiawan NFN, Yulizar Y, Simanjuntak P. The Synergy Effect of Azadirachtin and Minor Components of Neem Seed Oil on Antifeedant Activity of Spodoptera litura. Buletin Penelitian Tanaman Rempah dan Obat. 2019;30(1):27.
47. Bexrolli A, Shahini S. Using Spinosad as a bio-insecticide for controlling Tuta Absoluta (Meyrick, 1917). Proceedings of The 5th Virtual Multidisciplinary Conference; 2017/12/31: Publishing Society; 2017.
48. Campos EVR, de Oliveira JL, Pascoli M, de Lima R, Fraceto LF. Neem Oil and Crop Protection: From Now to the Future. Front Plant Sci. 2016;7:1494-.
49. Ragsdale DW, Voegtlin DJ, O'neil RJ. Soybean Aphid Biology in North America. Annals of the Entomological Society of America. 2004;97(2):204-8.
50. Liu J, Wu K, Hopper KR, Zhao K. Population Dynamics of *Aphis glycines* (Homoptera: Aphididae) and Its Natural Enemies in Soybean in Northern China. Annals of the Entomological Society of America. 2004;97(2):235-9.
51. Mordue AJ. Present Concepts of the Mode of Action of Azadirachtin From Neem. Neem: Today and in the New Millennium: Kluwer Academic Publishers. p. 229-42.
52. Vikrant, Singh DR, Kumar S, Kishor K, Kewal R. Bio-efficacy of Insecticides against Helicoverpa armigera in Chickpea. LEGUME RESEARCH- AN INTERNATIONAL JOURNAL. 2019(of).
53. Chapman RF. The Insects: Cambridge University Press; 1998 1998/11/12.
54. Rodrigues MP, Astoreca AL, Oliveira ÁAd, Salvato LA, Biscoto GL, Keller LAM, et al. In Vitro Activity of Neem (Azadirachta indica) Oil on Growth and Ochratoxin A Production by Aspergillus carbonarius Isolates. Toxins (Basel). 2019;11(10):579.
55. Chatterjee A, Saluja M, Singh N, Kandwal A. To evaluate the antigingivitis and antipalque effect of an Azadirachta indica (neem) mouthrinse on plaque induced gingivitis: A double-blind, randomized, controlled trial. J Indian Soc Periodontol. 2011;15(4):398-401.
56. Chava VR, Manjunath SM, Rajanikanth AV, Sridevi N. The Efficacy of Neem Extract on Four Microorganisms Responsible for causing Dental Caries viz Streptococcus mutans, Streptococcus salivarius, Streptococcus mitis and Streptococcus sanguis: An in vitro Study. The Journal of Contemporary Dental Practice. 2012;13(6):769-72.
57. Chattopadhyay RR. Possible mechanism of antihyperglycemic effect of Azadirachta indica leaf extract. Part IV. General Pharmacology: The Vascular System. 1996;27(3):431-4.
58. Abbas M, Nasir A, Kashif M, Hussain K, Bano N, Raza MA, et al. Serodiagnosis of toxoplasma gondii, associated risk factors in domesticated cats: preventing zoonosis in humans and implications for livestock extension. International Journal of Agricultural Extension. 2021;9(1).
59. El-Khoreiby A, Melouk A, Hafez N, Abd El-Salam N. INFLUENCE OF COLD STORAGE ON FRUIT QUALITY AND MARKETABILITY OF SOME PEACH CULTIVARS. Journal of Plant Production. 2011;2(1):127-37.
60. Oparaeke AM. Field screening of nine plant extracts for the control of post-flowering insect pests of cowpea, *Vigna unguiculata* (L.) Walp. Archives Of Phytopathology And Plant Protection. 2006;39(3):225-30.
61. Ogunwolu EO, Odunlami AT. Suppression of seed bruchid (Callosobruchus maculatus F.) development and damage on cowpea (Vigna unguiculata (L.) Walp.) with Zanthoxylum zanthoxyloides (Lam.) Waterm. (Rutaceae) root bark powder when compared to neem seed powder and pirimiphos-methyl. Crop Protection. 1996;15(7):603-7.

62. Sokame BM, Tounou AK, Datinon B, Dannon EA, Agboton C, Srinivasan R, et al. Combined activity of *Maruca vitrata* multi-nucleopolyhedrovirus, MaviMNPV, and oil from neem, *Azadirachta indica* Juss and *Jatropha curcas* L., for the control of cowpea pests. *Crop Protection*. 2015;72:150-7.
63. Rahman A, Talukder FA. Bioefficacy of some plant derivatives that protect grain against the pulse beetle, *Callosobruchus maculatus*. *J Insect Sci*. 2006;6:1-10.
64. Ahmad S, Ansari MS, Muslim M. Toxic effects of neem based insecticides on the fitness of *Helicoverpa armigera* (Hübner). *Crop Protection*. 2015;68:72-8.
65. Muhammad A, Malgwi AM, Nahunnaro H. Effect of Sowing Dates, Intra-row Spacings and Pesticides on *Maruca vitrata* (Fab.) (Lepidoptera: Pyralidae) Damage on Cowpea in Samaru, Northern Guinea Savanna. *Nigeria Journal of Entomology*. 2018;34(1):87-98.
66. Lowery DT, Isman MB, Brard NL. Laboratory and Field Evaluation of Neem for the Control of Aphids (Homoptera: Aphididae). *Journal of Economic Entomology*. 1993;86(3):864-70.
67. Pai MR, Acharya LD, Udupa N. Evaluation of antiplaque activity of *Azadirachta indica* leaf extract gel—a 6-week clinical study. *Journal of Ethnopharmacology*. 2004;90(1):99-103.
68. Anbalagan R, Srikanth P, Mani M, Barani R, Seshadri KG, Janarthanan R. Next generation sequencing of oral microbiota in Type 2 diabetes mellitus prior to and after neem stick usage and correlation with serum monocyte chemoattractant-1. *Diabetes Research and Clinical Practice*. 2017;130:204-10.
69. Chattopadhyay I, Nandi B, Chatterjee R, Biswas K, Bandyopadhyay U, Banerjee RK. Mechanism of antiulcer effect of Neem (*Azadirachta indica*) leaf extract: effect on H⁺-K⁺-ATPase, oxidative damage and apoptosis. *InflammoPharmacology*. 2004;12(2):153-76.
70. Chattopadhyay RR, Bandyopadhyay M. Effect of *Azadirachta indica* leaf extract on serum lipid profile changes in normal and streptozotocin induced diabetic rats. *African Journal of Biomedical Research*. 2006;8(2).
71. Manikandan P, Letchoumy PV, Gopalakrishnan M, Nagini S. Evaluation of *Azadirachta indica* leaf fractions for in vitro antioxidant potential and in vivo modulation of biomarkers of chemoprevention in the hamster buccal pouch carcinogenesis model. *Food and Chemical Toxicology*. 2008;46(7):2332-43.
72. Chaudhary S, Kanwar RK, Sehgal A, Cahill DM, Barrow CJ, Sehgal R, et al. Progress on *Azadirachta indica* Based Biopesticides in Replacing Synthetic Toxic Pesticides. *Front Plant Sci*. 2017;8:610-.
73. Bhat M, Kothiwale SK, Tirmale AR, Bhargava SY, Joshi BN. Antidiabetic Properties of *Azadirachta indica* and *Bougainvillea spectabilis*: In Vivo Studies in Murine Diabetes Model. *Evid Based Complement Alternat Med*. 2011;2011:561625-.
74. Priyanka Dash S, Dixit S, Sahoo S. Phytochemical and Biochemical Characterizations from Leaf Extracts from *Azadirachta Indica*: An Important Medicinal Plant. *Biochemistry & Analytical Biochemistry*. 2017;06(02).
75. Kamaraj C, Gandhi PR, Elango G, Karthi S, Chung I-M, Rajakumar G. Novel and environmental friendly approach; Impact of Neem (*Azadirachta indica*) gum nano formulation (NGNF) on *Helicoverpa armigera* (Hub.) and *Spodoptera litura* (Fab.). *International Journal of Biological Macromolecules*. 2018;107:59-69.
76. Kaverimaniyan V, Heuertz RM. Effects of Neem Extracts on Formed Biofilm of *Pseudomonas aeruginosa*. *The FASEB Journal*. 2020;34(S1):1-.
77. Bachchu MAA, Ara K, Uddin MN, Ara R. Larvicidal Efficacies of Four Indigenous Plant Extracts Against Red Flour Beetle, *Tribolium Castaneum* (Herbst) (Coleoptera: Tenebrionidae). *Journal of the Asiatic Society of Bangladesh, Science*. 2017;43(2):223-32.
78. Islas JF, Acosta E, G-Buentello Z, Delgado-Gallegos JL, Moreno-Treviño MG, Escalante B, et al. An overview of Neem (*Azadirachta indica*) and its potential impact on health. *Journal of Functional Foods*. 2020;74:104171.
79. Guidobaldi F, May-Concha IJ, Guerenstein PG. Morphology and physiology of the olfactory system of blood-feeding insects. *Journal of Physiology-Paris*. 2014;108(2-3):96-111.
80. Gadekar R, Singour PK, Chaurasiya PK, Pawar RS, Patil UK. A potential of some medicinal plants as an antiulcer agents. *Pharmacognosy reviews*. 2010;4(8):136-46.
81. Suleiman M, Yusuf MA. The Potential of Some Plant Powders as Biopesticides against *Sitophilus Zeamais* (Motsch.) (Coleoptera: Curculionidae) and *Callosobruchus maculatus* (F.) (Coleoptera: Bruchidae) On Stored Grains: A Review. *Bayero Journal of Pure and Applied Sciences*. 2012;4(2).
82. Somsak V, Chachiyo S. Antimalarial and Anti-hypoglycemic Properties of Siamese Neem Tree (*Azadirachta indica*) in *Plasmodium berghei* Infected Mice. *Malaria Control & Elimination*. 2015;4(2).

83. Xuan TD, Tsuzuki E, Hiroyuki T, Mitsuhiro M, Khanh TD, Chung I-M. Evaluation on phytotoxicity of neem (*Azadirachta indica*. A. Juss) to crops and weeds. *Crop Protection*. 2004;23(4):335-45.
84. Samar Raza T, Huma S, Alhamzah FA, Javed A. Revolutionizing Manufacturing with Blockchain Technology: Opportunities and Challenges. *International Journal of Online and Biomedical Engineering (iJOE)*. 2023;19(10):49-64.
85. Om O. Comparative Insecticidal Activities of some Botanical Powders and Pirimiphos-Methyl Against *Callosobruchus maculatus* Fab.[Coleoptera: Bruchidae] Infesting Cowpea Seeds. *MOJ Biology and Medicine*. 2017;2(4).
86. Olowu D. Agricultural transformation in Africa by the Winrock International Institute for Agricultural Development, 1993. Winrock international institute for agricultural development, 208 pp, US\$14.95. ISBN 0 933595 77 8. *Sustainable Development*. 1995;3(2):101-4.
87. Bandyopadhyay U, Biswas K, Sengupta A, Moitra P, Dutta P, Sarkar D, et al. Clinical studies on the effect of Neem (*Azadirachta indica*) bark extract on gastric secretion and gastroduodenal ulcer. *Life Sciences*. 2004;75(24):2867-78.
88. Arivoli S, Tennyson S. Antifeedant Activity Of Leaf Extracts Against The Adults Of Red Pumpkin Beetle *Raphidopalpa Foveicollis* Lucas 1849 (Coleoptera: Chrysomelidae). *Sustainability in Food and Agriculture*. 2020;1(1):15-20.
89. Anyaehie U. Medicinal properties of fractionated acetone/water neem (*Azadirachta indica*) leaf extract from Nigeria: a review. *Nigerian Journal of Physiological Sciences*. 2010;24(2).
90. *Synthesis of Natural Products from the Indian Neem Tree *Azadirachta indica**. American Chemical Society (ACS).
91. *PATENTS ON NEEM*. NEEM: Taylor & Francis.
92. *Current Research in Agriculture and Farming*.
93. *Book Reviews*. *Chemotherapy*. 1970;15(6):398-401.
94. Akhtar M. Biological control of plant-parasitic nematodes by neem products in agricultural soil. *Applied Soil Ecology*. 1998;7(3):219-23.
95. Salman M, Ganie SA, Saleem I. The concept of competence: a thematic review and discussion. *European Journal of Training and Development*. 2020;44(6/7):717-42.
96. Wong S-C. Competency definitions, development and assessment: A brief review. *International Journal of Academic Research in Progressive Education and Development*. 2020;9(3):95-114.
97. Hamel C, Michaud A, Thuku M, Skidmore B, Stevens A, Nussbaumer-Streit B, et al. Defining rapid reviews: a systematic scoping review and thematic analysis of definitions and defining characteristics of rapid reviews. *Journal of Clinical Epidemiology*. 2021;129:74-85.
98. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. *BMC medical research methodology*. 2008;8(1):1-10.
99. Chehri A, Yarani R, Yousefi Z, Shakouri SK, Ostadrahimi A, Mobasseri M, et al. Phytochemical and pharmacological anti-diabetic properties of bilberries (*Vaccinium myrtillus*), recommendations for future studies. *Primary care diabetes*. 2022;16(1):27-33.
100. Ferragina E, Seeleib-Kaiser M. THEMATIC REVIEW. *Policy & Politics*. 2011;39(4):583-611.