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## Review on: A Potential Natural Component for A Topical and Dermo cosmetic Products: Azadirachta Indica

Onkareshwar S. Kadam \*, Sanjay K. Bais

Fabtech College of Pharmacy, Sangola, Solapur, Maharashtra, India

\*Corresponding Author: onkareshwarkadam1@gmail.com

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### Abstract

*The broad-spectrum therapeutic properties of Azadirachta indica, popularly known as neem, have drawn a lot of focus in the dermo cosmetic industry. The process of photochemistry of neem and its applicability to skincare formulations are examined in this review, with particular attention paid to its bioactive ingredients, nimbin, nimbolide, and azadirachtin. Since these substances have anti-inflammatory, anti-microbial, wound-healing, and antioxidant qualities, neem is a promising natural ingredient for topical and dermo cosmetic products. In dermatology, the mechanisms of action of neem are examined, emphasizing its function in treating skin disorders such as psoriasis, eczema, and acne. Additionally, the formulation and development of neem-based products are examined in this review, along with the difficulties related to their stability, bioavailability, and efficient delivery systems. Analytical methods for evaluating the quality and composition of neem in dermo cosmetic formulations are described, including mass spectrometry (MS) and high-performance liquid chromatography (HPLC). Neem's future in dermo cosmetics is also examined, with an emphasis on new developments and consumers' increasing desire for sustainable and natural ingredients. There is also discussion of neem's toxicological issues, specifically its safe dosage and possible side effects. The review's conclusion highlights the need for more investigation into the long-term safety and effectiveness of neem in dermatological applications.*

**Keywords** – Dermo cosmetic sector, Phytochemicals, Emollient, Anti-Inflammatory qualities.

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### INTRODUCTION

#### The Growing Trend Toward Natural Ingredients in Dermo cosmetics

There has been a notable trend in the skincare and dermo cosmetic industries towards the use of natural and sustainable products. A growing number of consumers are looking for items made from plants because they are worried about the safety, effects on the environment, and possible negative consequences of synthetic chemicals. The demand for more ethical and clean beauty products that are therapeutic and kind to skin is what's driving this trend. Within this framework, plant-based substances have become more well-liked due to their effectiveness, safety records, and image as "green" substitutes. Of them, Azadirachta indica, or neem, is a well-known and adaptable natural active that has been used extensively in traditional medicine, especially in Ayurvedic and Unani systems.<sup>[1]</sup> Because of its strong bioactive components, neem has been used from ancient times to treat a broad range of illnesses, includes skin conditions. Neem's significance in dermo cosmetics has been re-examined in light of the growing scientific interest in herbal constituents. Its medicinal qualities, particularly its antibacterial, anti-inflammatory, anti-oxidant, and wound-healing capabilities, make it a desirable option for topical and skincare products.<sup>[2]</sup>

#### Neem Azadirachta Indica: An Overview

An evergreen tree native to the Indian region, currently planted throughout the world's tropical and sub-tropical regions, neem belongs to the Meliaceae family.

Given its extensive array of therapeutic applications, neem is frequently known as the "Village Pharmacy" in the India. The neem's entire body, including its seeds, oil, bark, and leaves, is full of beneficial bioactive substances. [3]



**Figure 1:** The Neem Tree (*Azadirachta indica*)

Of the more than 100 bioactive substances found in neem, azadirachtin, nimbin, nimbidin, and quercetin have been investigated the most. Neem is an effective medicinal agent because of these chemicals' antibacterial, anti-inflammatory, antioxidant, antifungal, and antiviral qualities. Neem has long been used as a treatment for fungus infections, psoriasis, acne, and eczema. Neem is being used more frequently in contemporary skincare formulas to treat conditions like inflammation, acne, hyperpigmentation, and ageing skin.

#### **Phytochemistry of Neem**

Neem's Effectiveness in Dermo cosmetic Treatments Stems from Its Rich Phytochemistry. The Principal Bioactive Constituents Consist Of:

##### **Azadirachtin**

A limonoid with strong antibacterial and insecticidal effects. In addition to being frequently used in pest management, azadirachtin helps lessen bacterial growth on the skin.

##### **Nimbin and Nimbidin**

The anti-inflammatory and antifungal effects of neem are attributed to these chemicals. Acne and eczema are among the problems they effectively treat since they help reduce oedema, redness, and irritation on the skin. [4]

##### **Quercetin**

A powerfully anti-inflammatory and antioxidant flavonoid. Two major causes of early ageing are oxidative stress and environmental damage, both of which quercetin helps shield the skin from.

##### **Fatty Acids**

Neem oil is rich in oleic, linoleic, or palmitic acids—essential fatty acids that have moisturising properties. These fats support the integrity of the skin's barrier, nourish the skin, and increase its ability to hold moisture.

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## Historical And Traditional Uses of Neem in Skincare

Neem has long been an essential component of Indian traditional skincare routines. Neem leaves were used to cure everything from minor cuts to serious diseases on the skin. The leaves were extracted into pastes, used as poultices, or boiled in water to be used as a bath. Because of its therapeutic qualities, neem oil, which was derived from the seeds, was administered straight to the skin. Neem branches were chewed for dental hygiene and neem water was applied topically as an antimicrobial in various cultures.<sup>[5]</sup> Neem is praised in traditional Ayurvedic writings as a "healing-all" herb, especially for skin conditions. It was thought to be a cooling herb that helped with skin detoxification, reduced inflammation, and aided in the healing process. Neem is still a key component of Ayurvedic skincare products today, especially those that balance out irritated pitta and kapha, doshas, which are frequently linked to inflammatory skin disorders like rashes and acne.

## Modern Applications of Neem in Dermo cosmetics

Neem is a useful element in contemporary dermo cosmetic formulations due its antibacterial, anti-inflammatory, and the anti-oxidant qualities. These days, neem oil and extracts can be found in many different products, such as moisturisers, toners, serums, cleansers, and sunscreens. Neem is frequently used in the following topical product applications:

### Acne Treatment

Neem is a useful treatment for pimples because of his antibacterial and anti-inflammatory characteristics. It not only lessens the irritation linked to pimples and cysts but also aids in controlling the growth of *Propionibacterium acnes*, a common bacterium that causes acne.<sup>[6]</sup>

### Anti-aging Products

The strong antioxidant content of neem aids in the elimination of free radicals and oxidative damage, which delays the onset of premature ageing. Neem oil's fatty acids help to maintain the hydration and flexibility of the skin, which lessens the visibility of wrinkles and fine lines.

### Eczema and Psoriasis Relief

Neem is perfect for treating inflammatory, dry, and itchy skin disorders including psoriasis and eczema because of its calming qualities. While its antimicrobial properties guard against secondary infections, its anti-inflammatory components soothe inflamed skin.<sup>[7]</sup>

### Fungal Infection Control

Athletes' foot and ringworm can be effectively treated with neem due to its antifungal characteristics, which also work against common fungal pathogens like *Candida albicans* and *Trichophyton rubrum*.

## Mechanisms of Action

### Antimicrobial Activity

One of neem's most well-researched characteristics is its antibacterial qualities. Azadirachtin and nimbidin are examples of compounds that function by rupturing the membranes of bacteria, preventing their growth, and ultimately causing the death of pathogenic germs. Neem is therefore very helpful in treating acne and other skin problems.

### Anti-inflammatory Effects

Many skin disorders, such as psoriasis, eczema, and acne, are characterised by inflammation. Neem's pro-inflammatory cytokine and enzyme inhibitory properties, including its inhibition of cyclooxygenase (COX) and lipoxygenase (LOX), are primarily responsible for its anti-inflammatory benefits. Neem helps lessen redness, swelling, and pain in affected locations by downregulating these inflammatory pathways.<sup>[8]</sup>

### Antioxidant Protection

The flavonoids and polyphenols found in neem, especially quercetin, neutralise the free radicals and decreases the oxidative stress. This shields of the skin cells from UV rays, pollution, and toxins, which are the main causes of skin ageing.

## Wound Healing

Neem stimulates collagen production and increases tissue regeneration, which speeds up the healing of small cuts and abrasions. Because of its capacity to lessen bacterial colonisation on the skin, it is especially helpful in the remedy of zits lesions and other skins injuries by lowering the risk of secondary infections.<sup>[9]</sup>

## Challenges and Considerations for Formulating with Neem

Neem has several obstacles when it comes to creating dermocosmetic products, despite its great benefits. The potent smell of neem oil, which turns off some customers, is one of the main problems. But developments in cosmetic technology have produced methods to reduce the odour without sacrificing Neem's healing properties. Furthermore, neem occasionally irritates those with sensitive skin, especially when applied in large amounts.<sup>[10]</sup>

Formulators also need to take into account the stability of the active ingredients in neem, since extended exposure to air and light can weaken the plant's effectiveness. This problem can be lessened by encapsulating Neem or adding it to sturdy, carefully prepared substrates.

## The Future of Neem in Dermocosmetics

Neem has a lot of potential in dermocosmetics as research into natural compounds keeps growing. According to recent research, neem may also help heal more serious ailments like rosacea, reduce hyperpigmentation, and enhance skin brightness. Neem is a great option for additional research into high-performance skincare products because of its sustainable and eco-friendly qualities, which are becoming more and more in demand in the global market for natural skincare products.<sup>[11]</sup>

## Method and Materials

### Methodology Overview

This review aims to objectively assess the safety, effectiveness, and use of *Azadirachta indica* (Neem) in topical and dermocosmetic products. The methods utilised to collect, examine, and compile pertinent information are described in this part, along with the resources consulted in evaluating neem's suitability as a natural active component in skincare products. There are multiple crucial steps in the evaluation process.

### Literature Review and Data Collection

A thorough search was carried out utilising databases like PubMed, Scopus, Google Scholar, and ScienceDirect to find peer-reviewed scholarly publications, clinical trials, and in vitro/in vivo research. The main search terms that were used were "*Azadirachta indica*", "Neem in skincare", "Neem's antimicrobial properties", "Neem's anti-inflammatory effects", and "Neem-based formulations."

### Inclusion and Exclusion Criteria

Studies on the topical uses of neem in dermatology and cosmetic research that were published during the last 20 years are included. Articles assessing the biological activity of Neem compounds, safety/toxicity information, and clinical trials involving Neem-based products were given special attention. Exclusion: Research that only examined neem's use in pesticide or agricultural applications, as well as publications lacking any experimental support.<sup>[12]</sup>

### Data Synthesis

The extracted data was categorised thematically according to attributes like antibacterial activity, anti-inflammatory effects, wound-healing capabilities, and possible skin irritation. After that, a compilation of the data was made to evaluate the usefulness of neem in different dermocosmetic applications.

### Neem Phytochemical Composition and Extraction

The components utilised in this research comprise numerous types of oils and extracts made from the leaf, seeds, bark, and flowers of the *A. indica* tree. Quercetin, nimbin, nimbidin, and azadirachtin are some of the bioactive substances of interest. Each ingredient gives distinct benefits to the skin, such as antibacterial and antioxidant characteristics.<sup>[13]</sup>

Bioactive Compound	Source	Biological Function	Dermocosmetic Application
Azadirachtin	Neem seeds	Antimicrobial, Insecticidal	Treatment for acne and skin infections
Nimbin	Neem leaves & Bark	Anti-inflammatory Antifungal	Reduces redness & swelling in skin disorder
Nimbidin	Neem bark & seeds	Antioxidant Antibacterial	Protects skin from oxidative damage,acne treatment

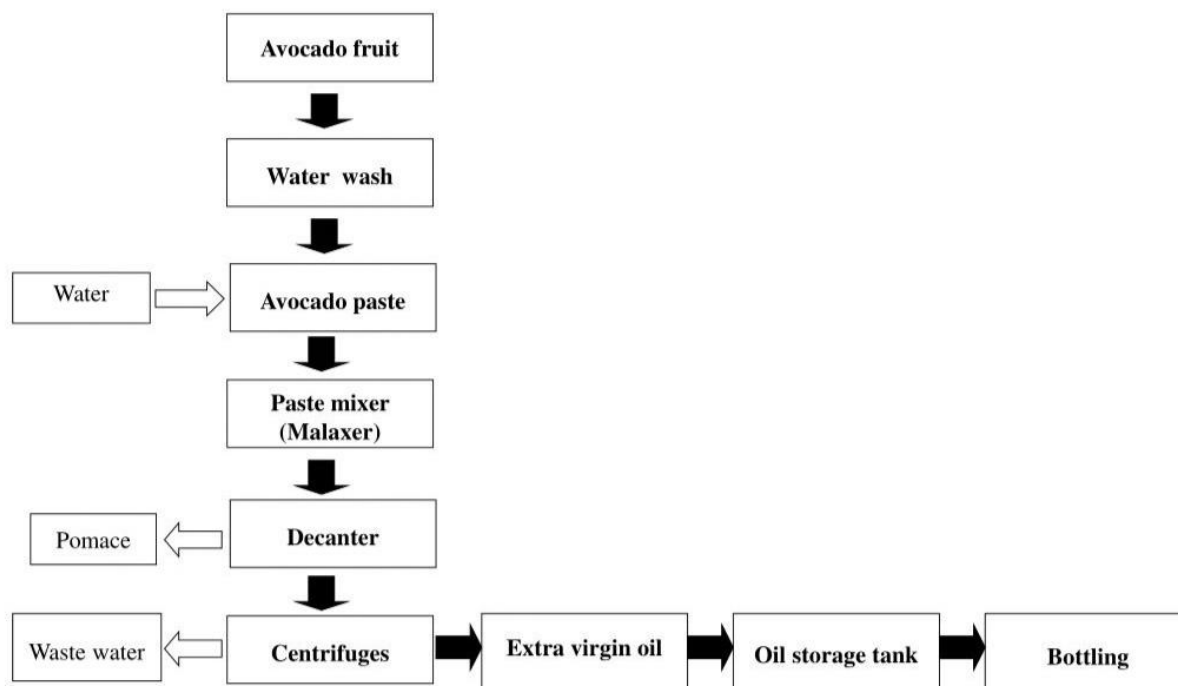
*Table 1: Key Bioactive Compounds in Neem and Their Skincare Benefits*

### Extraction Methods for Neem Compounds

The effectiveness and calibre of components derived from neem are greatly influenced by the extraction method. The phytochemical profiles obtained from various extraction techniques can have an impact on how well the resulting dermocosmetic compositions work. Neem is extracted primarily using two processes that are employed in cosmetics formulations:

#### Cold-Pressed Neem Oil Extraction

The process of cold-pressing entails mechanically removing oil from Neem tree seeds without using heat, maintaining the medicinal ingredients within the seeds. Because of its capacity to preserve vital fatty acids that nourish the skin, this approach is used in cosmetic compositions. Beneficial substances including azadirachtin and fatty acids are more concentrated in cold-pressed neem oil.<sup>[14]</sup>



*Figure 2: Cold-Press Extraction Process for Avocado Oil*

#### Solvent Extraction for Neem Leaf Extracts

To separate particular chemicals from Neem leaves, such as quercetin and nimbin, a solvent extraction technique is frequently employed. In order to dissolve the bioactive ingredients from dried Neem leaves, solvents like ethanol or methanol are used in the procedure. A concentrated extract full of antibacterial and anti-inflammatory properties is left behind when the solvent is evaporated during extraction.<sup>[15]</sup>

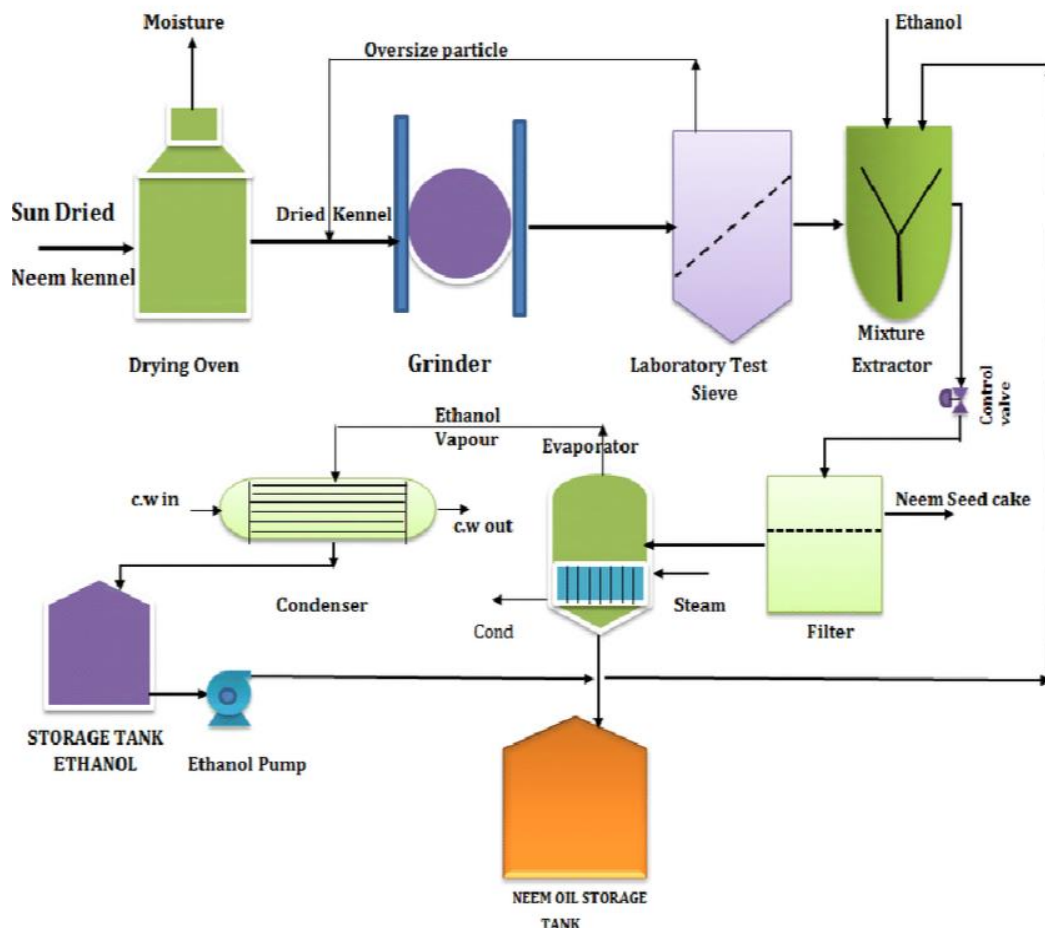


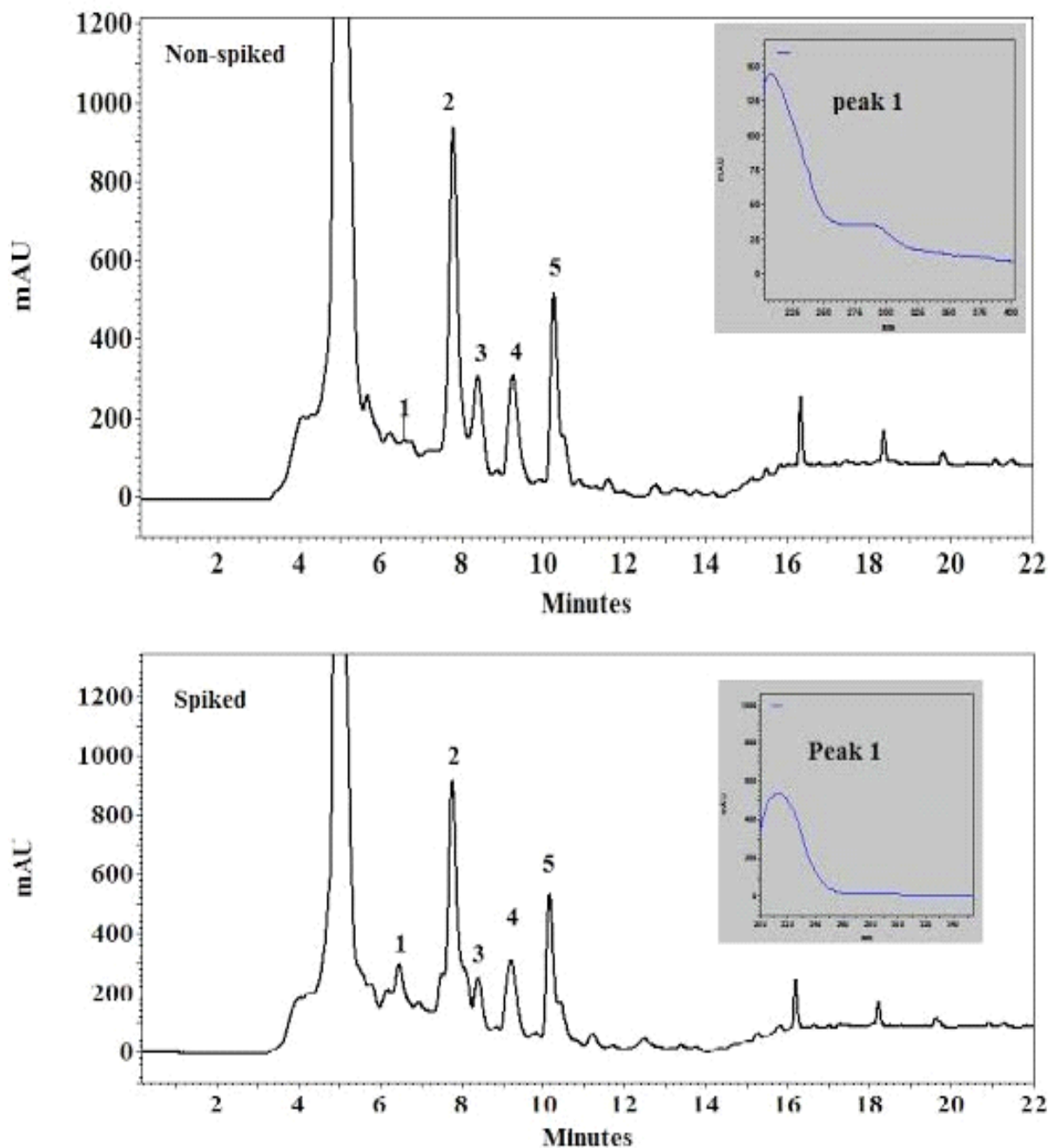
Figure 3: Solvent Extraction Process

**Analytical Techniques for Neem Composition**

Numerous analytical methods are employed to measure the amount of active components in neem extracts in order to guarantee their efficacy and purity in dermocosmetic compositions. The utilisation of these procedures guarantees the use of only premium extracts in beauty products and permits the standardisation of ingredients based on neem.<sup>[16]</sup>

**High Performance Liquid Chromatography**

Using HPLC, the content of nimbin, quercetin, and azadirachtin in extracts of neem is often determined. This method allows for the accurate quantification of each bioactive component by separating distinct molecules according to their molecular weight and polarity. The chromatogram below shows the separation of various phytochemicals in a Neem leaf extract.



**Graph 1:** HPLC Chromatogram of Neem Extract

**Gas Chromatography and Mass Spectrometry**

The content of fatty acid of neem oil is determined and quantified using GC-MS. Studying the makeup of Neem's essential oils is made possible by this method's exceptional efficacy in analysing volatile and semi-volatile chemicals.<sup>[17]</sup>

Fatty Acids	Percentage Composition
Oleic Acid (C18:1)	45%
Linoleic Acid (C18:2)	30%
Palmitic Acid (C16:0)	15%
Stearic Acid (C18:0)	5%
Other fatty acids	5%

**Table 2:** GC-MS Analysis of Neem Oil's Fatty Acid Profile

### Fourier Transform Infrared Spectroscopy

Neem extract functional groups are found via FTIR. This method generates a spectrum that can be used to pinpoint certain chemical bonds by measuring the extract's absorption of infrared light. Verifying the existence of specific bioactive groups, such as hydroxyl and carbonyl groups in flavonoids like quercetin, is very helpful with FTIR.

### Formulation Development of Neem-Based Products

Neem-based dermocosmetic product creation necessitates careful consideration of consumer safety, stability, and compatibility of ingredients. Several topical products can benefit from the inclusion of neem extracts, such as:

#### Neem-based Moisturizers

Emollient qualities of neem oil make it a popular ingredient in moisturising creams and lotions. 0.5% to 2% of neem oil is commonly added to formulations; this is enough to improve skin barrier function and hydrate without irritating the skin.<sup>[18]</sup>

#### Anti-acne Serums

Neem leaf extract is a common ingredient in anti-acne serums since it is high in antibacterial chemicals like azadirachtin. Typically, concentrations ranging from 1% to 3% are employed, and the extract is frequently mixed with other chemicals that combat acne, such as salicylic acid and tea tree oil.



*Figure 4: Neem-based Anti-acne Serum*

#### Neem-infused Cleansers

Neem extract has a mild antibacterial effect and can also be used to face cleansers. Neem is perfect for cleansers meant for skin that is prone to acne since it reduces inflammation and helps regulate the overgrowth of bacteria on the skin. Usually, these formulations have 0.5% to 1% neem extract in them.<sup>[19]</sup>

### Evaluation of Neem in Dermocosmetic Products

Following formulation, a battery of tests is conducted to assess the stability, safety, and efficacy of dermocosmetic products derived from neem. Common techniques for evaluation include of:

#### Microbial Efficacy Tests

Neem formulations are tested for their efficacy against common skin infections such as Propionibacterium acnes and Staphylococcus aureus using antimicrobial assays like agar diffusion and broth dilution techniques.

Pathogens	Inhibition Zone (mm)	Neem Concentration (%)
Staphylococcus aureus	15	2%
Propionibacterium acnes	18	1%
Candida albicans	12	2%

*Table 3: Antimicrobial Efficacy of Neem-based Formulations*



### Skin Irritation Tests

To guarantee that Neem formulations do not result in irritation or allergic responses, human patch testing are carried out. For the duration of these tests, a tiny patch of skin will be applied with the product, and after 24 to 48 hours, any indications of redness, swelling, or itching will be monitored.<sup>[20]</sup>

### Phytochemical Constituents of *Azadirachta Indica*

The medicinal benefits of neem (*Azadirachta indica*) in topical and dermocosmetic treatments are attributed to its diverse range of bioactive components. Phytochemicals found in the leaves, seeds, bark, and blossoms of the neem tree are responsible for its antiseptic, antioxidant, anti-inflammatory, and wound-healing compounds. Numerous bioactive substances, including polyphenols, flavonoids, limonoids, and essential fatty acids, have had their biological properties well studied.<sup>[21]</sup>

### Major Phytochemical Groups in Neem

#### Limonoids

The main sources of limonoids, a class of highly oxygenated triterpenoids, are neem seeds, bark, and leaves. The most well-known of these, azadirachtin, is an efficient antibacterial agent with insecticidal qualities. Other well-known limonoids, such as nimbin and nimbidin, have anti-inflammatory and antifungal properties that make them perfect for topical skincare formulations.

Compound	Source	Biological Activity
Azadirachtin	Neem seeds	Insecticidal, Antimicrobial
Nimbin	Neem leaves/bark	Anti-inflammatory, Antifungal
Nimbidin	Neem bark/seeds	Antibacterial, Antioxidant, Anti-inflammatory

*Table 4: Major Limonoids in Neem and Their Biological Activities*

#### Flavonoids

Flavonoids, which are well-known for their strong antioxidant capabilities, are abundant in neem leaves. Well-studied flavonoid quercetin is known for its anti-aging benefits since it is essential in scavenging free radicals and lowering oxidative stress. Kaempferol is an additional flavonoid that strengthens the skin's defence mechanisms against UV radiation and environmental contaminants.<sup>[22]</sup>

#### Polyphenols

Polyphenolic chemicals are abundant in neem leaves and bark. These substances work well in anti-aging formulas because they offer potent antioxidant protection and inhibit the deterioration of collagen.

#### Some Essential Fatty Acids

Here, the neem oil that is extracted from the seeds contains a lot of essential fatty acids, primarily oleic acid, linoleic acid, and palmitic acid. The preservation of skin moisture, enhancement of barrier function, and promotion of wound healing are all dependent on these essential fatty acids.

### Detailed Composition of Neem

Neem's phytochemical makeup changes according to the part of the plant that is utilised. The essential elements and their concentrations in the different sections of the Neem tree are outlined below.

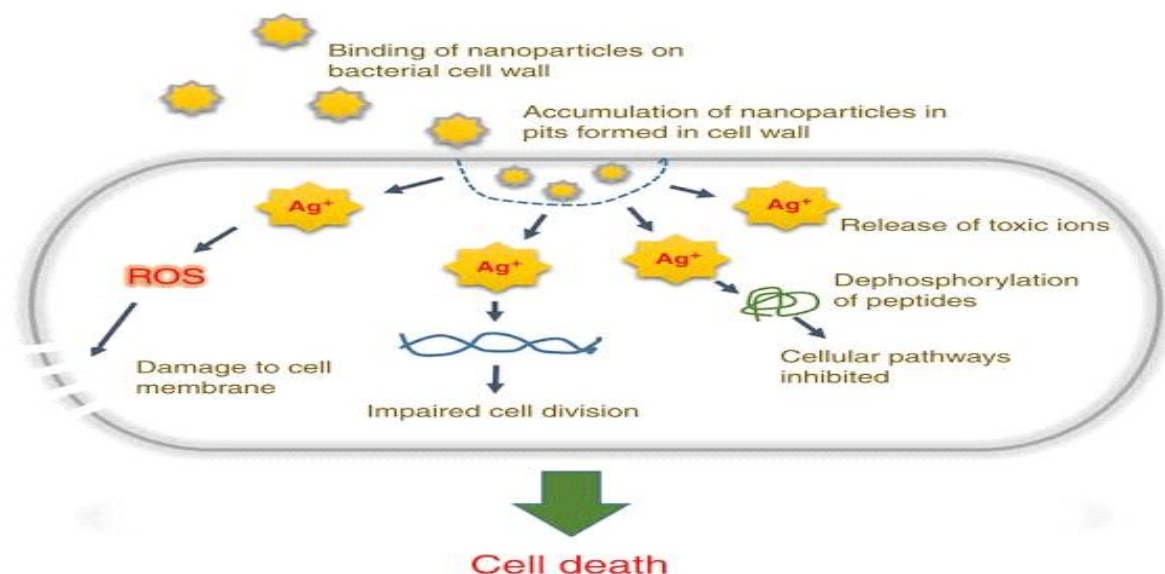
Neem Part	Key Phytochemicals	Biological Activity
Leaves	Quercetin, Kaempferol, Nimbin	Antioxidant, Anti-inflammatory, Antimicrobial
Seeds	Azadirachtin, Oleic acid, Linoleic acid	Antimicrobial, Emollient, Insecticidal
Bark	Nimbidin, Polyphenols	Antioxidant, Anti-inflammatory
Flowers	Flavonoids, Terpenoids	Antioxidant, Antifungal

*Table 5: Phytochemical Composition of Neem Parts*

## Mechanism of Action of Neem Phytochemical

### Antimicrobial Action

Neem is a great remedy for acne and other skin problems because it contains compounds like nimbin and azadirachtin that interfere with the moral strength of the bacterial cell membranes, inhibiting the growth of an bacteria.<sup>[23]</sup>



**Figure 5:** Antimicrobial Mechanism of Neem Compounds

### Antioxidant Action

Neem's flavonoids and polyphenols minimise oxidative stress on skin cells by neutralising free radicals by donating electrons. This system shields the skin from the elements and slows down the ageing process.

### Anti-inflammatory Action

In skin conditions like eczema and psoriasis, nimbin and nimbidin reduce redness and swelling by blocking pro-inflammatory enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX).

### Alternative Dermatological Effects

Rat wound destruction and laceration models are used to detect the curing potential of methanolic elicit from the leaves of neem and the *Tinospora cordifolia*. The elicit were found to have curing properties in the incision and the excision, the incision showing more potential for curing than the excision. The % of wound contraction and the resistance to the traction of the scar tissue were higher. Another skin conditions like pimples, an psoriasis, eczema, mycosis, and warts have all been treated with organic neem oil. In fact, the neem oil and leaves have been used by Indian ancient medicine from ancient times for cure skin related problems and the primarily psoriasis. Furthermore, intriguing new innovations incorporating the Neem and its skin related effects are developing; these technologies may have applications in the development of novel dermocosmetics. For example, the effect on dermatophyte development patterns and the anti-dermatophytic activity of *A. indica*'s leaf and the seeds were investigated. Substances extracted from the leaves and seeds of Neem were infected with *Trichophyton mentagrophyte*, *Microsporum nanum*, and *T. rubrum*. The least extract concentration that did not show any viable development after the incubation (21 days) is known as the minimum inhibitory concentration (MIC) value, whereas the least extract concentration that inhibits fungal development in the solid medium is known as MFC value. The examined fungi development pattern when exposed to neem elicit on Agar medium and the control were contrasted.<sup>[24]</sup> The remarkable anti-dermatophytic effects of neem leaf and seed extract were thus discovered.

As the oral controlled drug delivery system, however, the potential of *A. indica* in mucoadhesive polymer-containing microspheres generated by ionotropic gelation technique was assessed.

It is a better choice for the oral controlled drug delivery systems since in-vivo pharmacokinetic studies on animal (rabbits) showed an excessive number in mean residence time of 75% and relative bioavailability of one and half times. Furthermore, were efficacious against a variety of malignancy types, consisting both connective tissue and skin cancer. Embolide shown anticancer effect in animal experiments.

For example, nimbolide derived from neem at doses of five and twenty mg/kg dramatically suppress the employing in vivo as well as in vitro models, it was determined that the elements of neem development of mouse colon cancer xenografts. Furthermore, nimbolide-treated mice xenografts showed a marked decreased in the tumorigenic proteins, including those linked to invasion, angiogenesis, proliferation, survival, and metastasis. *Candida parapsilosis* and *Aspergillus niger* fungal culture tubes were more successfully inhibited by an ethosomal formulation including soy lecithin (300 mg), ethanol (35%), luliconazole (100 mg), and neem extract. A 24-hour release of  $83.45 \pm 2.51\%$  was shown in the same study's in vitro drug penetration test using a Wistar albino rat skin model. Neem extract and luliconazole therefore demonstrated synergistic benefits against fungal infections. Remarkably, a recent study revealed using *A. indica*, which is high in nimbidin, as a nutritional therapy for psoriasis. In an RCT (randomised controlled experiment) including 50 patients, the consumption of three capsules/day of *A. indica* resulted in a noteworthy decrease in the PASI (psoriasis area and severity index) score after 12 weeks. The authors speculate that nimbidin, a secondary biochemical present in the essential oil of neem, may have caused this by inhibiting prostaglandin synthetase.

#### **Toxicology Issues Related to Neem**

The information presented relates to the toxicological characteristics of *A. indica* species and concerns limonoids that, seed oil, and leaf and bark extracts. Animal studies represent the majority of the earliest and initial data because they were conducted in a period before alternative research approaches have developed in the present. REACH (The application, Evaluation, Approval, and Restriction of Chemicals), an organisation governed by EU law, also has the majority of this data registered. These publicly accessible data can be used to understand the toxicological character of neem and related phytochemical constituents, negating the need to repeat earlier finished safety tests.<sup>[25]</sup> The Organisation for Economic Cooperation and Development, or OECD, reported that the primary testing for Neem and its constituent parts revealed the following results, accounting for the safety of Neem for human health: genotoxicity, mutagenicity, inhalation toxicities, reproductive toxicity, eye irritation, skin sensitisation and irritation, acute oral harmful effects, subacute oral toxicity, acute dermal toxicity, and germination. Regarding the classification of ocular irritation, research found that when male New Zealand albino rabbits' eyes were treated with 0.1 mg of an ethanolic elicit of neem seed or an aq. solution containing 1% or 5% sodium nimbidinate, neither serious damage of eye nor irritation reaction was seen. Furthermore, a further investigation conducted in the same settings as previously described using a 10% aqueous solution of sodium nimbidinate demonstrated that the material injected into the guinea pigs' eyes did not cause any itching. As a result, there is no scientific proof that *A. indica* may irritate the eyes. Furthermore, an additional investigation revealed that when intradermally applied to albino rabbits, Margosan-O, an approved Neem-based pesticide, induced low-to-medium primary skin irritation. Margosan-O included a concentrated ethanolic elicit Neem seeds at 3000 ppm of azadirachtin ( $\pm 10\%$ ).

In the evaluated situations, this category indicates that the substance is a skin sensitizer. According to studies on acute oral toxicity, methanolic elicitation of Neem leaf and peel, when administered orally to rats, showed a lethal dose 50 (50% oral lethal dose) of around 13 g/kg of animal, causing the rodents to die from a violent terminal seizure.

In addition to refusing the food and drink, the study found that the animals that survived had gastrointestinal spasms, cold, and lethargy. These studies on acute oral toxicities in rats corroborated those of another investigation that found that when both rabbits and rats were administered oral neem seed oil, their lethaldose 50 over a 24-hour period was 14 and 24 mL/kg. To evaluate the long-term oral toxic effects in rodents, a made with alcohol remedy containing nimbidin at 25, 50, and 100 mg/kg was given as a single daily dose in the meals of male Holtzman rats for six weeks. The study found that there were no appreciable negative impacts on the rodents over the study period. Additionally, when the drug was given to albino rabbit via enhanced ethanolic extract MargosanO®, acute cutaneous toxicity testing revealed that the drug's lethal concentration was 50% higher than 2 mL/kg. In a study, male albino mice were given three different dosages of an aqueous extract of neem wood ash (5, 50, and 100 mg/kg total body weight) to determine its reproductive toxicity.<sup>[26]</sup> The gonadosomatic index, sperm count, motility and morphological analysis of sperm, serum levels of luteinizing (LH) and the follicle-stimulating (FSH) hormones, testosterone assay, and testicular histopathological observations were among the parameters assessed. Even in the absence of a negative impact on testosterone, testicles weight, or hormones such as FSH and LH, the results showed a significant decline in movement and sperm count. Furthermore, a different study looked at how reproductive toxicity affected poultry (*Coturnix coturnix japonica* L.) fed for 60 days with varying quantities of neem seeds added to the meal (0, 5, 10, 20, and 40%).<sup>[27]</sup> According to the study's findings, there were notable variations in the number of sperm, seminal volume, vigour, motility, and viability. The scientists came to the conclusion that *A. indica* should be highly hazardous to reproduction as a result of these two trials. Additionally, nimbidin's teratogenic profile was assessed in a different investigation. It assessed the effects of administering an additional ten percent water-soluble solution of nimbidin solutions at 25, 50, and one hundred milligrams per kilogram to viable rats who had paired for 13 days. Chronic anatomical abnormalities in the foetus were the examined parameter. According to the study's findings, the organs of the newborn pups were normal even when the largest doses were administered. Consequently, breeding performance did not suffer as a result. Nimbidin does not appear to have any teratogenic effects, in conclusion. Since there was no proof that *A. indica* or its phytochemical components posed a health risk to humans for the intended use, toxicological data for these chemicals recommended that they might be applicable in dermocosmetic formulations. On the other hand, no scientific researches were available on the safety of neem and its composition in terms of things like phototoxicity and carcinogenicity. Therefore, more toxicological testing is still required to broaden the scope of these compounds' safety. <sup>[28,29,30]</sup> An investigation of toxicological data regarding the sustainability of *A. indica* revealed that, in contrast to the toxicological records found for its safety for human health, this chemical and its separate elements could be highly dangerous to the environment. Furthermore, all dermocosmetic knowledge has to validate the toxicological defense of the crucial formula, ahead of time safety of probable interaction, or strengthening of adverse reactions related with the chemical-based, even if based on toxicological data of each of the components. *A. indica* extracts' most current in vivo toxicity is also reviewed, with two primary sections: (a) aqua species toxic effects and (b) mammals (rats, animals such as rabbits etc.) toxicity. These sections conclude with possible novel therapeutic medicine and pesticide applications, respectively. More importantly, research has shown and validated the medicinal properties of *A. indica*, even calling it the “village pharmacy” or the “doctor’s tree”. *A. indica* is therefore a fantastic option for pilot research examining dermocosmetic efficacy. <sup>[31]</sup>

## CONCLUSION

Neem is a great natural active for topical and dermocosmetic uses because of its many therapeutic effects from its phytochemical ingredients. Neem's vital fatty acids, limonoids, and flavonoids are among the compounds that contribute to its powerful anti-bacterial, anti-inflammatory, antioxidant, and the skin-healing abilities. These bioactive substances not only improve the health of the skin but also deal with common dermatological problems like irritation, ageing, and acne. Due to its rich phytochemistry, neem is certain to remain relevant in contemporary dermocosmetic formulations despite the increasing consumer demand for herbal skincare products.

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