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BIO-PESTICIDE, NEEM OIL AS A BETTER ALTERNATIVE IN PLACE OF SYNTHETIC PESTICIDE FOR SAFE AGRICULTURAL PRACTICES AND ENVIRONMENTAL SUSTAINABILITY – A REVIEW

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Abstract-

Unfavorable changes that affect the environment, known as environmental pollution, are mostly the result of human activities and can arise directly or indirectly from changes in radiation levels, energy patterns, chemical and physical makeup as well, and the preponderance of creatures. As a result, we are gradually but certainly degrading our planet to the point that life is disappearing at an extremely concerning rate. Agrochemicals known as pesticides are employed in urban green spaces, public health initiatives, and agricultural operations to protect plants and people from numerous illnesses. During the monsoon and land runoff, synthetic pesticides are drained into the nearby water bodies in the system. Of these synthetic pesticides, only 1% truly kill the insects and other pests; the remaining 99% end up in the water, on our food, and in the atmosphere. However, both naturally occurring and man-made toxins do significant harm to aquatic ecosystems. The main drawbacks of pesticides are including their toxicity to some animals, useful plants, and humans, and the persistence (long life) of some of these toxins in the environment. When these pesticides enter aquatic ecosystem, became the environment costs. Fish, the largest and most varied species of vertebrate fauna, are an important part of the food chain, and any pollution could harm the nutritional value of fish and humans who eat them. In order to maintain the sustainability of society and our ecosystems while safeguarding them from the use of these dangerous pesticides, it is now more evident than ever that a new agricultural idea related to food production must be put into practice. Utilizing bio-pesticides provides an environmentally acceptable way to handle pest management to support agricultural activities.

Neem oil has emerged as the most well recognized plant-based bio-pesticide due to its ability to prevent plant disease resistance caused by synthetic insecticides and to create a sustained pest resistance mechanism. Neem (*Azadirachta indica*) oil is extracted from the seeds and fruits of the neem tree, which is indigenous to the Indian subcontinent and has spread too many other tropical regions. The potency of pure neem oil is incredible. It is the most beneficial of the neem's commercially accessible compounds and is utilized in organic farming and medicine. Azadirachtin, the primary ingredient in neem oil, influences the hormone balance of both pests and insects, impacting their abilities to reproduce, hatch, eat, and other aspects of their regular life cycle. In this case, bio-pesticides can be used to reduce insect populations in a safer manner than synthetic pesticides. The characteristics of neem oil include immunological modulation, antiseptic, antiviral, antifungal, antibacterial, anti-parasitic, antiulcer, anti-arthritic, anticancer, anti-malarial, and spermicidal effects. An organic gardener also uses neem oil in their garden. Neem oil is a staple in Indian first aid kits, where it is used to cure a wide range of illnesses. Neem oil helps plants grow by 15-20% as well because it doesn't contain any chemicals. In order to make it safer for both humans and other aquatic environments, bio-pesticides like neem oil can be used in place of synthetic pesticides. The success of present and future bio-pesticides could be increased through enhanced research focusing on the usefulness of bio-pesticides over synthetic pesticides.

Key words- synthetic pesticide, bio-pesticide, neem oil, agriculture, environmental sustainability

I – INTRODUCTION

Toxic substances like pesticides have always caused sickness and death to coexist with the lives of humans, animals, fish, and other living things. Managing pesticide contamination is therefore one of the most important environmental challenges. Excessive pesticide usage is a feature of modern intensive agriculture and a contributing factor to the decline of farming systems. The unintended impacts of pesticides are one of the main operators of the adverse impact of modern industrial cultivation on whole environment. The environmental impact of agribusiness differs widely based on practices employed by agriculturists and by the scale of practice. Farming communities that try to decrease environmental hazards through modifying their practices will adapt sustainable agriculture

practices. The environmental effects of pesticides describe the broad series of consequences of using pesticides. By eliminating unwanted plants, fungus, and insects, they reduce agricultural landscape biodiversity to just one food crop. Since soil resilience is directly impacted by biodiversity deficiencies, this kind of crop management has long-term negative implications on agricultural systems (Mesnage and Séralini, 2018). According to estimates from the UN Food and Agriculture Organization (FAO), increases in yields and the number of times a crop can be grown on the same land annually will account for 80% of the food production increases required in developing nations to keep up with population growth. The increase of farmed area is estimated to provide just 20% of the new food production. Because they can stop significant crop losses, pesticides will always be used in agriculture. Nonetheless, there is always worry about how pesticide exposure affects both the environment and people.

Regardless of the economic standing of the area, the use of pesticides in food production both for local consumption and export should adhere to appropriate agricultural practices. Farmers have to use no more pesticide than is absolutely required to save their crops. In some situations, it is also feasible to grow food without using pesticides. In India, fishing has been a valuable economic activity for a very long time. Fish are thought to be reliable indicators of aquatic contamination. Changes in the quality of the water affect them quite much. Furthermore, measurements of these parameters may be applied to fish toxicity as changes in biochemical parameters signify modifications in the organisms' metabolic and biochemical processes.

Bio-pesticides rely on complementing biological methods as well as chemical and biochemical methods (Michelle *et al.*, 2014). Researchers are more inclined to utilize natural or plant-based pesticides, such as bio-pesticides, to manage pests because synthetic pesticides are the primary source of environmental issues. Because of its ability to effectively manage pests while causing little danger to the environment or human health, neem oil is widely acknowledged as a bio-pesticide. Neem oil is made from the seeds of the neem tree (*Azadirachta indica*), is a very biologically active plant that is highly recognized for its ability to repel insects which is indigenous to the Indian subcontinent and commonly known as “village dispensary” for its many more properties as medicinal, fertilizer, plant protectant and lubricant. Main chemical constituents of neem oil which performs its significant role are shown in the figure (1).

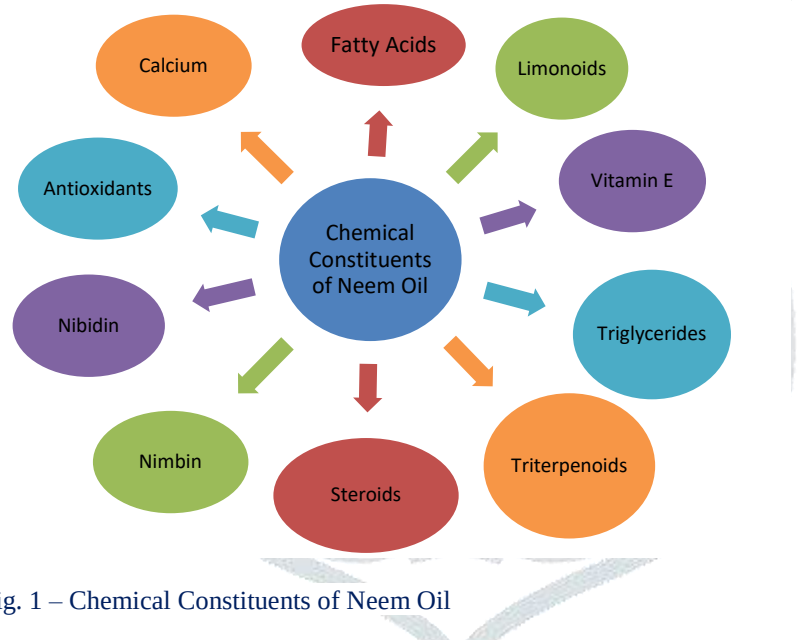

Fig. 1 – Chemical Constituents of Neem Oil

It has a number of chemicals that have antibacterial, growth-disrupting, and insect-repelling properties. For many years, neem oil has included the triterpenoid active component azadirachtin and second triterpenoid called nimbin whose antibacterial, antiviral, antifungal, antipyretic, and antihistamine effects have been well-established (Kraus, 1995; Harikrishnan, *et al.*, 2003). It is worth replacing dangerous synthetic pesticides since it is natural, safer, easier to use, and more affordable (Bond *et al.*, 2012). Azadirachtin was historically used to treat a wide range of illnesses and is now a commercially viable substance (Das, Mukherjee and Murjani, 2002). Azadirachtin is often applied based on the manufacturer's indicated technical qualities (EC %) and used every 10–15 days, depending on the situation. In ambient circumstances, azadirachtin is stable for less than a week (Sundaram, 1996). In water exposed to sunlight, azaridachtin has a half-life of 36–48 hours (Scott and Kaushik, 2000). Moreover, it has shown effective in managing fish predators in aquaculture locations. It has been discovered to be harmful to species that are not its intended targets, and it causes noticeable changes in test animals (Mondal, Barat and Mukhopadhyay, 2007). Restrictions and limits on the use of neem oil products are frequently enforced by regulatory organizations to reduce possible dangers to aquatic creatures, particularly fish. These rules outline application schedules, rates, and buffer zones to reduce the amount of neem oil residues that come into direct contact with water bodies. Regulatory entities usually enforce regulations to reduce the negative effects of neem oil on the environment. These regulations usually include limitations on the pace at which the oil is applied, the creation of buffer zones surrounding bodies of water, and detailed instructions for using the oil in agriculture in a way that protects aquatic ecosystems. Here are some best proposals of neem oil as an alternative of synthetic pesticide is described as follows (Fig. 2).

Fig. 2- Best Proposals of Neem Oil -

As per the Verified Market Report (2023), the size of this market was estimated at USD 1396.67 million in 2023 and is projected to grow at a compound annual growth rate (CAGR) of 13.48% between 2024 and 2030 to reach USD 3758.62 million by the end of that year. Owing to customers' growing preference for natural and sustainable goods across several industries, the market for neem oil is now seeing a surge in demand. Because it is environmentally safe and has many applications in the domains of agriculture, cosmetics, and healthcare, neem oil is gaining popularity as a versatile solution. As more people become aware of neem oil's benefits which include skin care and pest control the market for the product is expanding. Neem oil stands out as a safer alternative to synthetic pesticides, aligning with modern agricultural trends towards sustainability and reduced environmental impact. Its multifaceted benefits make it a valuable tool in maintaining crop health while preserving ecological balance in farming ecosystems. As research continues to explore its potential and optimize its application, neem oil is poised to play a crucial role in promoting sustainable agricultural practices worldwide. Neem oil has garnered significant attention from researchers due to its potential as a bio-pesticide offering safer agricultural practices and environmental sustainability.

II – Benefits of Neem Oil in Agriculture:

Here are some key areas of interest and findings related to neem oil in agricultural research:

1. **Biodegradability and Non-toxicity**: The duration of a pesticide's presence in the environment is referred to as its persistence. This is dependent upon the rate of degradation, which is mostly determined by the chemical makeup and surroundings. It may build up in fish and endanger both people and other animals. When utilized properly, neem oil is non-toxic to birds, animals, and helpful insects like bees. It also decomposes rapidly in the surroundings. As a result, there is less chance of dangerous residues in water and soil. The primary ingredient of azadirachtin, neem oil, is biodegradable and demonstrates very low toxicity to mammals and other species. It reduces the possibility of a long-term buildup in fish tissues and implies it degrades in the environment more quickly than synthetic pesticides. As opposed to synthetic pesticides, which may linger in the environment and build up in food chains, this feature helps preserve ecological balance and lessens long-term environmental effect. Neem oil breaks down into less hazardous byproducts than the parent chemicals in most cases. Neem oil leftovers are often decreased within days to weeks, depending on environmental factors such as temperature, pH, and microbial activity, according to studies that have examined the breakdown routes of neem oil in water and soil settings.
2. **Broad-spectrum Pest Control**: The number of articles about the application of neem oil, to manage agricultural pests has increased significantly over the last ten years (Gahukar, 2014; Bakry *et al.*, 2016). Neem oil affects the eating, molting, and reproductive cycles of insect pests, hence disrupting their growth and development, according to studies. It has proven effective against over 200 different insect species, including beetles, aphids, whiteflies, thrips, leafminers, mites, and caterpillars. The most active component of neem oil, azadirachtin, contains tetran or triterpenoids and functions similarly to the hormones "ecdysones" of insects, preventing them from growing further or laying eggs. This ultimately disrupts the insects' entire life cycle, and other components of neem oil prevent insects from feeding, which eventually results in their death. It can be used as a larvicide and repellant for termites, ants, bedbugs, cockroaches, houseflies, sandflies, snails, and mosquitoes in residential settings (Franco, *et al.*, 2017). The outer muscle layer of cockroaches is also broken down by neem oil, causing them to avoid contact with it and cease visiting the area owing to its unpleasant odor. A combination of neem oil with entomo-pathogenic microorganisms was much successful against vegetables sucking pests.

3. **Reduced Harm to Non-Target Organisms:** Neem oil poses no harm to beneficial insects, birds, mammals, and other non-target animals, but it is selectively toxic to pests. By protecting populations of pollinators like bees and naturally occurring pest predators, this trait aids in the preservation of biodiversity. Because it preserves the natural dynamics of predator-prey relationships, it also helps ecosystems remain resilient. The applications and benefits of neem oil for gardening were discussed by Balcony Garden Web (2021). Neem oil-loaded zein nanoparticles did not have an impact on soil nitrogen-fixing and denitrifying bacteria, according to research on the impact of neem oil on non-target soil microbiota (Pascoli *et al*., 2019). The review conducted by Adhikari *et al*. (2020) focused on the possible applications of neem extract, byproducts, and functions as a bio-pesticide in agriculture.

4. **Resistance Management**: Neem oil functions through a variety of mechanisms of action, preventing pests from gradually developing resistance, in contrast to synthetic pesticides that have the potential to cause insect resistance. The potential of neem oil to reduce insect resistance is another topic of interest for study. Because synthetic pesticides only contain one active toxin, they differ from natural pesticides in this regard. Additionally, it poses a risk for insects and pests to develop tolerance to the many active poisons included in bio-pesticides. An insect or pest can only produce one resistance gene every generation. To build diverse resistance genes that can withstand all of the active toxins found in synthetic pesticides is also a lengthy and laborious process. Neem oil is less likely to cause target pests to develop resistance due to its complex composition and several mechanisms of action than conventional pesticides, which frequently cause resistance in pests. Neem oil is so efficient against pests that it remains effective even after several applications in the garden. Neem oil never develops immunity in insects or pests, thus it's always effective against them.

5. **Integrated Pest Management (IPM**): Integrated pest management (IPM) tactics, which seek to reduce the use of chemical pesticides and implement sustainable farming practices, rely heavily on neem oil. Together with crop rotation, biological controls, and cultural methods, neem oil helps farmers control insect populations efficiently and use less chemicals overall. By using these all-encompassing methods, the effects on aquatic ecosystems are reduced, long-term agricultural production is supported, soil health is improved, and natural resources are preserved.

6. **Nutrient Enhancement**: Neem oil has been shown to increase plant nutrient absorption and soil fertility, resulting in stronger, healthier growth. Additional advantages of neem oil for agriculture have been studied; they include its capacity to increase soil fertility, improve plant nutrient absorption, and enhance crop health in general. Rich in potassium (1- 4%), nitrogen (2–3%), and phosphorus (1%), it has the potential to be a source of organic manure. By lowering the need for artificial fertilizers and pesticides, these agronomic advantages support sustainable agricultural methods. Synthetic pesticides deplete the fertility of our fertilizer soil and leave it barren. Additionally, neem oil takes a long time and a complex procedure to generate various resistance genes that can withstand all of the active poisons that are present in the synthetic pesticide (Jika and Tolong 2021). Its therapeutic and pesticidal properties are widely known. Without largely depending on artificial fertilizers, it can increase plant resistance against environmental stresses and function as a growth stimulator, resulting in better harvests. Because better soil health lowers soil erosion and sustains soil fertility and structure over time, it also supports sustainable farming methods. The ability of the soil to release active ingredients gradually gives plants nutrients that encourage development (Mala *et al.*, 2016), which has the potential to completely transform the bio-pesticide sector.
7. **Safety for Farmers and Consumers**: Neem oil is a safe and environmentally friendly alternative to synthetic pesticides, as it can be applied without heavy protective gear, reducing the risk of exposure. Its low toxicity to people and animals reduces health hazards for farmers, customers, and workers handling treated products. This safety profile promotes sustainable agriculture operations and promotes safe working conditions. However, even after thorough cleaning, some pesticide residue remains in the plant, posing severe health risks. Plant-based medicines and their derivatives are increasingly popular worldwide for disease treatment and prevention. Neem oil and its constituents are used sparingly in food preservation, packaging, and coatings, making them both environmentally and human health-friendly. Fruits and vegetables can be packaged using chitosan, starch, or pectin in combination with neem oil or its nanoemulsion. A review provides an overview of neem oil and nanoemulsion for food preservation and packaging, including its chemistry, functional characteristics, advanced delivery system, and various uses (Kumar *et* al., 2022).
8. **Environmental Sustainability**: Neem oil supports sustainable farming practices by encouraging organic pest management and lowering dependency on artificial pesticides. By maintaining populations of helpful insects and creatures, it promotes biodiversity. The low toxicity of neem oil to non-target creatures, such as birds, mammals, and helpful insects like bees, makes it a highly praised substance. Assessment of its environmental destiny, paths of degradation, and possible effects on soil health and aquatic ecosystems has been the main areas of research. Neem oil provides a more environmentally friendly substitute for synthetic pesticides by lowering chemical residues and pollution in the environment. In order to guarantee reliable and efficient pest control while upholding environmental safety, researchers are always improving application procedures.
9. **Mode of Action:** Neem oil, containing azadirachtin, has been found to have insecticidal properties due to its active ingredients. Researchers have studied its effects on hormone regulation, eating behavior, development stage disruption, and other biochemical and physiological processes that affect pests. The physiological effects of azadirachtin are more consistent than the anti-feedant effects. The dosage response effects in all insect species include delayed molts, aberrant molts, higher mortalities, and decreased growth. The disrupted endocrine system, causing molting effects, is linked to the disturbance in the production and release of ecdysteroids. To maximize benefits and reduce side effects, neem oil compositions and administration methods have been optimized.

III – Impact of Neem Oil on Freshwater Fishes –

Aquatic toxicology is a study of the effects of environmental pollutants on aquatic organisms such as effect of pesticides on health of fishes or other aquatic organisms. The impact of neem oil on fishes is a topic of concern, especially in aquatic ecosystems where pesticide residues can potentially affect non-target organisms. Here are some key points regarding the impact of neem oil on fishes based on available research:

1. Acute Toxicity

According to studies, neem oil typically has minimal acute toxicity to fish, which means that fatal dosages are rather large and accidental exposure is unlikely to result in immediate injury. On the other hand, long-term exposure or sensitive species may cause negative consequences. Fish usually show no acute toxicity to neem oil when it is used in agriculture at the appropriate quantities. According to studies, under typical exposure circumstances, the active ingredient in neem oil, azadirachtin, has a relatively low toxicity profile for fish species. The variations in LC_{50} values can be attributed to several factors, such as the concentration, time of exposure, sensitivity to the toxicant, type and size of the experimental animal, and so on. The acute toxicity levels of several bio-pesticides for a wide variety of fish species reported by many researchers.

According to Cagauan *et al*. (2004), the communicating 96-hour LC_{50} values were 2.57 and 3.0 ml/L, and the fatal concentration of neem was 12.4 ml/L for Nile tilapia *Oreochromis niloticus* L. and 8.31 ml/L for mosquito fish *Gambusia affinis* Baird and Girard. Bioneem oil (90% neem oil and 10% emulsifiers and synergistic compounds) was studied for acute toxicity against *D. magna* and *D. rerio* for 48 and 96 hours of exposure, respectively, by Maranho *et al*. (2014). The median effective concentration (EC50) for immobility in the instance of *D. magna*, subjected to varying concentrations of bioneem oil, was found to be 0.17 ml/L, while the LC_{50} value for *D. rerio*, following varying dosages of bioneem oil, was found to be 0.22 ml/L. Thus, they deduced that *D. magna* had higher sensitivity to the bio-insecticide than *D. rerio*. From the studies presented and highlighted in review of Braga *et al*., (2021) cleared that for aquatic organisms, neem extracts presented the lowest toxicity, while neem pesticides or derivatives presented moderate to high toxicity. However, these extracts have been tested only in terms of acute toxicity, thus chronic studies need to be performed in future. Although only a few studies on aquatic animals were mentioned, it can be said that the application of neem commercial pesticides should be handled with care and aqueous neem-based products should be encouraged. Parvin and Shukla (2023) investigated that at highest concentration of nuvan (15 ml/20L) all fishes died within 96 hours. However, at the maximum concentration of neem oil (25 ml/20 L), 80% of the fish perished after 96 hours. When compared to neem oil, nuvan had a more harmful impact at lower concentrations for *Clarias batrachus*. Since neem oil has a higher LC_{50} value than nuvan, it is thought to be less harmful to non-targeted creatures, such as fish. Lethal dosages are usually far greater than those seen under routine agricultural operations, yet fish may show transient behavioral alterations or modest behavioral changes if exposed to high concentrations.

2. Chronic Effects

Although there are few studies on chronic exposure, some evidence points to possible long-term effects on fish health from extended exposure to neem oil or its byproducts in water. Sub-lethal consequences like changed eating habits, growth rates, or success in reproduction may fall under this category. Nevertheless, after application, the concentrations needed to produce these effects are usually greater than those found in aquatic settings. The effects of neem oil on fish liver, blood, lungs, gills, and kidneys are not well documented in studies or firsthand data. But still, based on the properties of neem oil and related studies, here are some considerations:

According to research by Oniovosa *et al.* (2017), the African catfish (*Clarias gariepinus*) was able to tolerate neem leaf extract given by feed at sub-lethal dose with little to no negative effects on organ histology, biochemical parameters, or haematological indices. Neem oil is sometimes referred to as a "immunomodulator," which means that when the immune system gets deregulated, it helps the inborn immune system's capacity to self-regulate (Herbal Secrets, 2020). Because of their effective function in boosting immunity against specific fish illnesses and inhibiting the growth of specific pathogens, the use of *Azadirachta indica* seed extracts in the fish business has been encouraging. Neem (*A. indica*) boosts primary and secondary immunological responses in fish (*Oreochromis mossambicus*), according to Logambal and Michael (2001). Neem oil's effects on fish blood are not extensively documented, but its components could potentially affect blood parameters such as oxygen transport or immune function if absorbed in significant quantities. Much research has been switched on natural immune stimulant and their potential to protect from diseases in various fish species, as various parts of neem plant (Martinez, 2002; Winkaler *et al.*, 2007) amongst others. According to Hassanein *et al.* (2007), environmental contamination with trilogy (neem biopesticide) in *Ctenopharyngodon idella* caused biochemical alterations in proteins and DNA. Triology's 96-hour LC_{50} value was discovered to be 112 ppm. The acute toxicity of neem oil, according to Ramachandramohan and Mamatha (2015), is low and has less of an influence on skin structure. It may also have less of an impact on the number of gobies in the habitat—the Cauvery delta region of Karnataka, India—than an organophosporus insecticide. The development of bio-pesticides based on *Azadirachta indica* as a substitute for synthetic hazardous pesticides was documented by Chaudhary *et al.* (2017). Neem oil's hepato-protective effects in *Clarias gariepinus* are demonstrated by a progressive decline in AST and ALT levels, as reported by Oniovosa *et al.* (2017).

Anti-oxidant effects of azadirachtin play an important role in protective mechanisms of neem against metabolic syndrome and its complications. Neem oil was described as having a strong antioxidant impact by Rinaldi *et al*. (2017). They also proposed that neem oil has a structural function and has protective properties, making it an essential component for the stability and preservation of neem oil nanoemulsions. Feed containing *Azadirachta indica* is more efficient than feed including regular other components in boosting the immunity of fish fingerlings, as shown by Patel *et al.* (2021). Neem will boost fish growth and survival rates when added to other

substances in fish food. Neem oil contains azadirachtin and other compounds that could potentially affect liver and kidney function in fish if they accumulate in these organs. These effects could include metabolic changes or impairment of detoxification processes, but significant impacts would likely require prolonged exposure to high concentrations compare than synthetic pesticide. The protective effects of *Azadirachta indica* (neem) against metabolic syndrome with a special focus on mechanisms reviewed by Yarmohammadi *et al.*, (2021). According to research by Yarmohammadi *et al.* (2021), neem's anti-oxidant properties and over-expression of the transcription factor nuclear factor erythroid 2–related factor 2 (Nrf2) allow it to regulate hypertension and hyperglycemia. Furthermore, Abidin *et al.* (2022) reported that the biochemical and hematological examination of *Clarias gariepinus* was determined to be within the normal range, with higher levels of total proteins, globulin, and lymphocytes indicating immunological activation against certain pathogenic pathogens. Neem's anti-inflammatory and antioxidant qualities may aid in the reduction of oxidative stress, hence enhancing the health of the kidneys and liver (Hallal, 2021).

IV - Impacts of Neem Oil on Mammals –

Because neem oil comes from a plant, most people assume that it poses no damage to human health or the environment. To guarantee the safety of developed neem oil-based formulations for use in sustainable food preservation, packaging, and storage, toxicity testing of neem oil and neem oil-based natural pesticides and insecticides is required (Deng, *et al.*, 2013). Deng, *et al.*, (2013) reported a mice model with an LD_{50} (lethal dosage responsible for 50% mortality) of around 32 g/kg, and discovered that the animals' eating habits did not change substantially from the control group even at that high oral dose of neem oil. In a related investigation, oral administration of azadirachtin extracted from neem oil to male and female rats at dosages for 90 days produced no changes in tissue weight, pathology, serum and blood parameters, or symptoms of toxicity (Raizada *et al.*, 2001). The advantage of these animal models is that they include human traits including placentation, fetal development, and interactions and metabolism between the mother and the fetus that are absent in some other models (Hansen, 2012). Mice, rats, and rabbits comprise the majority of the mammalian model organisms.

After 90 days of sub-chronic toxicity testing, Wang *et al.* (2013) found no mortality, no impacts on body weight, and no statistically significant changes in the mice's blood biochemistry markers as compared to the control group. Additionally, there was no statistically significant change in the organ coefficients of the liver, heart, lung, kidney, and spleen between the treated and control groups of mice; nevertheless, at larger dosages, the mice displayed clinical indications associated with the therapy. After the therapy was stopped for thirty days, the damages that were seen were repaired. In addition, Bansod *et al.* (2020) observed no appreciable differences between the nimbolide-treated and control groups in terms of body and pancreatic weight and plasma biomarker levels Vepacide, a neem-based insecticide, was given orally to rats for 45 or 90 days as part of a sub-chronic exposure. Rahman and Siddiqui (2004) investigated the biochemical consequences of this treatment. These modifications showed that lung tissue was the most vulnerable, followed by the liver and kidney. These changes were dosage and time dependent. However, the animals recovered after 28 days of treatment (withdrawal trial), suggesting that the toxic symptoms would go away if the toxicant was eliminated. The antioxidant content of pure neem oil was high. Because of its antioxidant capabilities, it is therefore frequently employed in several pharmaceutical companies to treat a wide range of ailments (Kumar and Navaratnam, 2013). Neem is available as a dietary supplement in plant based mixture in North America. Hsia *et al.*, (2004) treated with this dietary supplement (2 capsules 3 times per day) in type 2 diabetic patients (the ages of 18 and 70) for 3 months, improved glucose control and HbA1c levels were noted. Kochhar *et al.*, (2009) investigated the antidiabetic effect of neem in 90 diabetic men 40 to 60 years of age and resulted that neem reduces sweating, itching, polydipsia, headache, burning feet, and polyphagia in diabetic patients.

V – Use of Neem Oil for Medicinal Purposes–

Ayurvedic folk medicine has long used neem oil (Franco *et al.*, 2017). Because of its cooling qualities, it is utilized to balance the Pitta and Kapha doshas. There is insufficient data to support its application in managing acute cutaneous damage associated with cisplatin-based chemotherapy for head and neck cancer (Meeran *et al.*, 2013). Additionally, it helps minor wound healing due to its antibacterial and healing qualities. As oil, it includes a variety of substances, such as fatty acids (EFA) that are beneficial to the skin, such as oleic, linoleic, and palmitic acids, and antioxidants (Jamie Eske, 2019). It lowers inflammation while also promoting cell flexibility and turnover. It is an excellent anti-aging treatment due to the synergistic action of hydrating triglycerides and antioxidants like vitamin E and carotenoid. (ruralteasures.com). Numerous components in neem oil are incredibly good to the skin (Kitty Jay, 2019). As a result, the oil is a common component in skin care products that help treat a variety of skin conditions, including ringworm, warts, psoriasis, acne, eczema, and all forms of skin aging. In contrast to conventional pesticides, neem oil is anti-cancerous and does not cause cancer. Furthermore, several scientific investigations are underway to comprehend its protective impact against cancer. Because neem oil contains azadirachtin, which is a natural insecticide, the Environmental Protection Agency (EPA) noted that neem oil is a "low toxicity" material. That could result in allergic responses, such dermatitis from touch. Neem oil is used by certain practitioners of traditional Chinese and Ayurvedic medicine to cure a variety of ailments, including fungal infections and ulcers. As a result, because of these safety features and their established pharmacological qualities, neem tree and its extracts present a high commercial significance and can be considered serious candidates to new natural drugs therapies.

VI – Toxicity of Neem Oil –

Many researchers analyzed the toxicity of neem oil specifically. According to Groot *et al.* (2017), neem oil consumption has the potential to be toxic and can result in metabolic acidosis, convulsions, renal failure, encephalopathy, and severe brain ischemia in newborns and young children. Neem oil should not be taken by itself without consulting a physician, especially in case of pregnancy,

attempting to conceive, nor have young children. Additionally, according to Ashok *et al.* (2013), it may be connected to allergic contact dermatitis. Numerous studies have demonstrated that fish may have histological and biochemical abnormalities as a result of exposure to bio-pesticides (Chandra and Khuda-Bukhsh, 2004; Winkaler *et al.*, 2007). Parveen *et al.* (2004) reported the reduction of acetylcholinesterase activity in several fish tissues as well as the impact of neem seed bio-pesticide, neem-2100, on *Tilapia mossambica*. Yadav *et al.* (2019) evaluated the protective effects of leaf extract from *Moringa oleifera* on zebra fish that were exposed to neem oil toxicity via *Danio rerio* induction. In their four-day acute bioassay test, 130 adult zebra fish were chosen at random, subjected to different neem oil concentrations, and the fatality rates were noted. Continuous investigation and observation are essential to guarantee the sustainable application of neem oil in farming methods without jeopardizing the health of aquatic ecosystems and to get a deeper understanding of the long-term impacts of neem oil.

VII – Challenges and Considerations:

While neem oil degrades quickly, frequent applications may still affect non-target organisms and soil micro-biota. Regulations vary by country regarding the use of neem oil, with some jurisdictions requiring specific formulations or usage guidelines.

VIII – Conclusion –

Neem oil is a crucial tool for promoting environmental sustainability in agriculture due to its biodegradability, low toxicity to non-target animals, and support for biodiversity. It is also incorporated into integrated pest management (IPM) tactics, ensuring a more robust and sustainable food production system. Thus neem oil plays a significant role not only in regulating insects and pests but also in helping to address the long standing problems of pesticide resistance in agriculture. Neem oil has minimal acute toxicity to fish and other animals, and smaller dosages can avoid sub-acute and sub-chronic toxicity. However, it is not as harmful to aquatic life as synthetic pesticides, and its potential effects on fish organs should be thoroughly examined. Current research indicates that neem oil minimizing the harmful impacts of synthetic pesticide and have less or non toxic impacts to the fish, and when used normally in agriculture and in compliance with legal requirements. Further study is needed to understand its mechanisms of action, improve application methods, and increase its applicability in various global agricultural systems. Overall, neem oil's potential as a key component of sustainable agriculture is significant, and further research is needed to fully understand its potential benefits.

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