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Review Article

Mitragyna parvifolia (Roxb.) Korth.: Phytochemistry, Ethnopharmacology, and Therapeutic Potential

Rishita Shrivastava*, Kuldeep Singh, Dr. Arvind Kumar Srivastava, Nitesh Dubey

Shambhunath Institute of Pharmacy, Prayagraj, Uttar Pradesh

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ABSTRACT

The Rubiaceae family tree Mitragyna parvifolia, (Roxb.) Korth., commonly referred to as Kadamba, Kaim, has a long history of usage in Ayurvedic, Unani, & folk medicine. Historically, various plant parts have been utilized to treat gynaecological diseases, ulcer-related fever, inflammation, rheumatism, and jaundice. Numerous bioactive substances, including as flavonoids, tannins, glycosides, sterols, and indolic & oxindolic alkaloid (mitraphylline, isomitraphylline, and rhynchophylline), have been identified by phytochemical investigations and contribute to its medicinal properties. Its ethnomedicinal claims are supported by pharmacological tests that confirm a wide range of actions, including antiulcer, analgesic, anti-inflammatory, antioxidant, antibacterial, antidiabetic, antihypertensive, anticonvulsant, antiproliferative, & anticancer properties. With methanolic extracts exhibiting LD_{50} values exceeding 5000 mg/kg or ethanolic extracts tolerating up to 2000 mg/kg in rats with no significant side effects, toxicological assessments demonstrate a wide margin of safety. There is currently insufficient data on long-term safety, chronic toxicity, & clinical efficacy in people. The current body of knowledge regarding M. parvifolia ethnopharmacology, phytochemistry, pharmacological activity, and safety profile is compiled and critically examined in this review. In addition to highlighting the need for additional mechanistic, toxicological, or clinical research to create standardized phytomedicines, the findings also point to its therapeutic promise, notably in antiulcer therapy.

INTRODUCTION

Mitragyna parvifolia, sometimes referred to as Kadamba or Kaim, is a member of the Rubiaceae family. Their excellent timber is used as an ornamental tree in the surrounding area. It has the potential to heal a number of old illnesses and viral infections, with a particular focus on COVID-19, using traditional medicinal plants. Numerous human ailments have been significantly treated by

***Corresponding Author:** Rishita Shrivastava
Address: *Shambhunath Institute of Pharmacy, Prayagraj, Uttar Pradesh*
Email ✉: rishitashrivastava562@gmail.com
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Mitragyna parvifolia, and several phytoconstituents have been shown to prevent the spread of many viruses. It is very important to determine which of the many metabolites found in plant material makes it a viable option for an antiviral medication. [1] Several plant-based antiviral chemicals, including as alkaloids, flavonoids, terpenoids, amino acids, lignans, polysaccharides, and polyacetylenes, are effective against several viral targets, including DNA, RNA, genomes, membranes, replication, and ribosome function. The Kadamba tree is a wonder with significant pharmacological implications. India is frequently referred to as a botanical paradise because it produces the most Ayurvedic medicinal herbs worldwide.

Different plant parts of *Mitragyna parvifolia*: (Fig. 1) Leaves, (Fig. 2) Fruit, (Fig. 3) Seed, (Fig. 4) Bark.

One of the most widely planted trees in the tropical area is Mitragyna parvifolia (Family: Rubiaceae). Roads and pavements are lined with Kadamba to provide shade.

The plant flourishes in both deciduous and evergreen woods all throughout India. The plant's chemical components include aldehydes, ketones, pyroligneous acid, and methyl acetate. [4]

This plant's fruit juice is used to help nursing moms produce more breast milk. Plant leaves are applied to ulcers and wounds to reduce pain and swelling and promote healing.[5]

This plant's bark and roots are used as an aphrodisiac and to cure gynaecological diseases, fever, colic, burning sensations, muscle discomfort, poisoning, cough, and edema. Its leaves are applied to wounds and ulcers to reduce pain and swelling and promote healing. [6]

Approximately 70% of Western Rajasthan, which includes the "12" districts, is covered by the Indian Thar Desert. It would turn out to be essential for any efforts to restore and preserve Mitragyna parvifolia. (Roxb.) Korth. [7]

Rationale And objectives of the Review:

Mitragyna parvifolia, (Roxb.) Korth. is a significant medicinal plant that has long been used to cure a variety of illnesses, such as ulcers, fever, inflammation, or gastrointestinal issues, in Ayurvedic, Unani, and folk medical systems. The scientific information on its phytochemistry & pharmacological effects is still sparse and scattered, despite its broad ethnomedical significance. Although evidence for flavonoids, alkaloids, terpenoids, and various other bioactive chemicals has been documented in a number of studies, no concerted attempt has been made to critically assess and incorporate these discoveries with its traditional usage and medicinal applications.

Furthermore, there are few thorough studies that highlight the promising therapeutic effects suggested by pharmacological investigations like antiulcer, antioxidant, hepatoprotective, or antibacterial activity. In this situation, a thorough review is required to provide a solid foundation to future drug development by bridging the gap between conventional knowledge and contemporary pharmacological validation.

Therefore, the current review aims to summarize and analyse the existing information regarding the botanical, ethnopharmacological, & phytochemical features of *M. parvifolia*, as well as compare it to other Mitragyna species; identify research limitations; highlight future perspectives for its growth in the field of standardized phytomedicine; and summarize its pharmacological & therapeutic potential with a focus on antiulcer activity.

Taxonomical Classification:

Kingdom	Plantae
Sub kingdom	Tracheophytes
Phylum	Magnoliophyta
Class	Magnoliatae
Order	Rubiales
Family	Rubiaceae
Genus	Mitragyna
Species	*Mitragyna Parvifolia (Roxb) korth*

Synonyms of Mitragyna Parvifolia along with their different Names:

Bionomical Name	*Mitragyna parvifolia (Roxb.)* Korth
Scientific Name	*Mitragynaparvifolia (Roxb.)* Korth *MitragynaparvifoliaVar.Parvifolia NucleaparvifoliaRoxb. Nucleaparvifoliawild [Illegitimate] Stephegyle Parvifolia (Roxb.) Korth*
English	Burflowertree, Kaim, Laran and Leichhardt pine
Hindi	Guri, kaaylum, kaddam, Kadambkaim, Kayim
Marathi	Kalam
Gujrati	Kalam
Bengali	Dharakadam, Gulikadam
Kannad	Kadaani, Kadagada, Kadavala, kongu, Nayekadambe, Neerkadamba, Sannakadamba
Malayalam	Kadamba, Rooskatamp, Kathamamaram, Neerkadambu, Rosekadambu, Poochakadambu, uccakkatamp, Sirakadambu, Sirikadamba, Veembu, Vimba, Vimpu.
Nepali	KaimPhalduSaanoHaledo, Tikul
Sanskrit	Irula- kadambamaram, Vitanah
Tamil	Katampai, Niculam, Nirkatampu
Telgu	Ajaghnamu, Ambusaramu, Jalatumburu, Nirkadamba, Rsya, Tadhidruma

Religious Tree:

According to ancient literature, this "true Kadamb" is connected to Lord Krishna at Vrindavan instead of the well-known *Neolamarkia cadamba* tree. There is no doubt that this is an instance of mistaken identity. While ***Mitragyna parvifolia*** is not just native to the Vrindavan forest but also the dominating tree there, the species *Neolamarkia cadamba* doesn't exist natively in the hot, arid Vrindavana region. In Vrindavan, ***Mitragyna parvifolia*** can still be found practically

everywhere. The tree should be referred to as Haripriya (God's favourite) since the same seems to apply to mother goddess Durga, who lives in Kadam Forest. It is referred to as Lord Krishna's favourite tree. [8]

Graphical Distribution:

Originating in India, the plant is widespread throughout Asia and Africa's tropical and subtropical zones. The more well-liked areas are the Himalayas, Kerala, Karnataka, Assam, and western India. Other nations that have it include Pakistan, Nepal, Sri Lanka, Myanmar, and Indonesia. Tall and graceful, Mitragyna parvifolia has a spread crown and a range of medicinal properties. [9]

ETHNOPHARMACOLOGY AND TRADITIONAL USES:

Native Americans and other ayurveda practitioners utilize the plant extensively since it is said to have countless medical benefits.

This plant's bark is utilized in Ayurveda to cure conditions involving the blood. The bark of the plant can be utilized to make phytomedicine that is profitable. Worm expulsion is another usage for the plant. For muscle aches, a bark paste is used externally. To alleviate toothaches, cooked bark is inhaled into the mouth together with fruits. [10]

The Chenchus, Yerukalas, Yanadis, & Sugalis from Gundur District, Andhra Pradesh, use the sap from fresh leaves of Mitragyna parvifolia to treat jaundice. Its leaves promote improved wound and ulcer healing and reduce pain and edema. Local residents in Tumkur district, Karnataka, India, use the stem bark of M. parvifolia to alleviate muscle aches and biliousness. [10]

Tribes in Sonaghati, Sonbhadra district, Uttar Pradesh, use a bark decoction of M. parvifolia to treat fever. The stem bark, M. parvifolia is used to treat rheumatic discomfort by the Valaiyans, a tribe that lives in the Sirumalai Hills in the Madurai district of the Western Ghats in Tamil Nadu. Its bark and roots are used as an aphrodisiac and to cure gynecological diseases, fever, colic, burning sensations, muscle discomfort, poisoning, coughing, and edema. (11) The fruit juice acts as a lactodepurant and increases the amount of breast milk produced by nursing moms. Timber is utilized in the paper industry, furniture, and farming tools, among other things. [12]

PHYTOCHEMICAL CONSTITUENTS:

Alkaloids, flavonoids, tannins, and glycosides are produced by the stem and bark. Bark alcohol extract contains phenols, tannis, alkaloids, polysaccharides, and phytosterols. Sterols, phenols, and carbohydrates were obtained from benzene extracts. Mitraphylline, isothitraphylline, pteropodine isopterepodine, speciophylline, and uncarine F are the six main oxindolic alkaloids found in leaves. Rotundifoline, rhynocophylline, isorotundifoline, rhynchociline, speciocilitine, speciofoline, and mitragynine are other plant alkaloids. Additionally, the plant produces methyl acetate, pyroligneous acid, aldehydes, ketones, scopoletin, thermophyllinedaucosterol, quinovic acid, and β-sitosterol.[15]

The leaves of the Mitragyna parvifolia plant contain two alkaloids, 16, 17-dihydro-17 β hydroxyl isomitraphylline & 16, 17, dihydro-17 β hydroxyl mitraphylline, which are both reasonably priced. The primary alkaloid component was mitraphylline. Tetrahydroalstonine, akkyamigine, hirsuteine, and other indolic and oxiindollic alkaloids are found in the tree's ariel portions, stem, bark, and roots. [28]

In young plants cultivated from Ceylon seed, the preliminary distribution of the alkaloid pattern in

Mitragyna parvifolia revealed that the trunk bark contains the open-cell E ring alkaloids isorhynchophylline or rhynchophylline in addition to the closed E ring alkaloids that include akuammigine, pteropodine, isopteropodine, speciophylline, and uncarine F. [13]

Only rhynchophylline and isorhynchophylline were found in the root bark. Isorhynchophylline, rhynchophylline, and corynoxeine are found in the root's xylem and phloem components. The root phloem also contains hirsutine and hirsuteine (also known as Als-hirsutine). A more thorough analysis of the seeds or seedlings as well as every part of a young plant produced from seed has shown an intriguing pattern of the alkaloids throughout the whole plant. [14]

The leaves of Mitragyna parvifolia have been shown to contain a variety of oxindolic and indolic alkaloids. The principal oxindolic alkaloids identified from Mitragyna parvifolia that have been reported from the Lucknow region are only six: Mitraphylline, Isomitraphylline, and Pteropodine, Isopteropodine, Speciophylline, and Uncarine F. Other alkaloids present in the plant include rotundifoline, rhynchophylline, the isorotundifoline compound, rhynchociline, speciociliatine, speciofoline, and mitragynine. In addition to alkaloids, the plant contains pyroligneous acids, ketones, and aldehydes. scopoletin, thermophyllin, and daucosterol, quinovic acid, β-sitosterol, and methyl acetate. [15]

An ethanolic solution of M. parvifolia plants treated with an acid-base chloroform fraction yielded a total four hetero yohimbine class oxindole alkaloids. According to their spectroscopic results and a comparison with the literature, 16, 17-dihydro-17b-hydroxy Isomitraphylline was identified, 16, 17-dihydro-17b-hydroxy mitraphylline, isomitraphylline, and mitraphylline, respectively. Heteronuclear singular quantum coherent experiment with direct coupling (HSQC), heteronuclear multiple bonds correlation spectrum (HMBC), and 1H- H correlated spectroscopy (COSY) Were used to clarify the structures of 1 and 2. To determine the amount of sp, sp2, sp3, & quaternary carbon atoms, the DEPT. experiment was employed.[11]

PHARMACOLOGICAL ACTIVITIES:

Certain substances have been identified by researchers as the cause of specific pharmacological occurrences. Together with two known alkaloids, isotriphylline and mitraphylline, the leaves of the plant M. parvifolia have produced two alkaloids: 16,17-dihydro-17b-hydroxyisomitraphyline and 16,17-dihydro-17b-hydroxymitraphylline. A few of these alkaloids have local anesthetic properties, especially mitraphylline and mitragynine. Researchers looked at M. parvifolia extracts, especially ethanolic that methanolic extracts, which show antibacterial activity against specific bacterial strains and are realistically useful for creating new antimicrobial agents. [16]

The leaves and stem barks of M. parvifolia have been found to contain a variety of indolic and oxindolic alkaloids, such as dihydrocorynantheol, akuammigine, mitraphylline, and rhynchophylline. These alkaloids have been shown to have analgesic, antiarthritic, antipyretic, anti-inflammatory, antinociceptive, anticonvulsant, anxiolytic, anthelmintic, anti-microbial, antiproliferative, and antioxidant activity. It has been established that the alcohol-based extract from M. parvifolia tree fruit contains anthelmintic properties. The population of the species in question is endangered in some locations because of its immense relevance in many facets of medicine, culture, industry, and ecology. But because of its status, it is spread via a variety of techniques, including

micropropagation, in order to achieve therapeutic value. [17]

Antiulcer Activity:

According to the study, ethanolic extracts of M. parvifolia Roxb. at 400 mg/kg considerably enhanced the anti-secretory, cytoprotective, and ulcer healing effects. The plant's antiulcer properties were assessed using the pylorus ligation method. [18]

Antibacterial and Antifungal Activity:

The extract at varying concentrations Antibacterial activity was evaluated using the agar-based well diffusion method. The plant extract did not demonstrate antibacterial activity versus bacteria such as Bacillus subtitis, Escherichia coli, or pseudomonas aeruginosa. However, it did considerably inhibit five aureus and demonstrated some degree; inhibition of Paeruginosa and E. coli (A).[19]

Analgesic, Antimicrobial and Anti-inflammatory Activity:

The extract at a dose from 500 mg/kg ($P<0.01$) demonstrated potent analgesic effects comparable to the standard medicine Diclofenac sodium 50 mg/kg using the hot plate method, while the acetic acid-induced writhing test and Eddy's hot plate were used to test the analgesic activity in Swiss effects albino male mice. M. P. ethanolic extract was tested for its antibacterial, analgesic, and anti-inflammatory properties. [20]

Anticonvulsant Activity:

Ethanolic extract from Mitragyna Parvifolia leaves has an anticonvulsant action. was examined by examining the impact of maximal electroshock convulsive techniques and seizures brought on by phenylenetetrazole (PTZ) in mice. Mice were given three oral dosages of the extract (100, 250, and 500 mg/kg); only the 500 mg/kg dose showed a protective effect. Consequently, the results indicated that both models were dose-dependent. [21]

Anthelmintic activity:

When tested for anthelmintic action against pheritimaposthuma, the ethanolic and aqueous extracts of Mitragyna Parvifolia leaves showed a substantial paralysis, worms at higher concentrations of 50 mg/ml when compared to albendazole (10 mg/ml) as a standard reference. Significant anthelminstic activity was created by a methanolic extract, dried stem bark at a concentration of 100 mg/ml. This activity was assessed by measuring the earthworms' paralysis and death times, and it was discovered that the effect was dose dependent; a lower concentration of 20 mg/ml produced no results. The paralysis and death times of earthworms were observed in comparison to the piperazine citrate standard, and the anthelmintic activity of the methanolic or ethanolic extract from *M. Parvifolia* fruit was found to be dosage dependent. [6]

Anti – Diabetic Activity:

M. Parvifolia yielded the indole alkaloid DHIM. DPP IV was significantly inhibited by DHIM. Chronic treatment of DHIM significantly decreased plasma glucose concentration and enhanced glucose tolerance in responses to glucose loading. In in vivo research on newborn Wistar albino rats given STZ, treated diabetic rats showed considerably higher levels of GLP-1 and IL-1. According to the assay, DHIM promotes cell division, decreases pancreatic cells, and increases the production of β-cells. [22,23]

Antiviral Activity:

An extract from *Mitragyna parvifolia* was tested against the bovine herpes virus type 1, which causes infectious bovine rhinotracheitis, abortions in cows between months five and seven of pregnancy, and significant financial losses. These plant extracts' BHV-1 antiviral properties were evaluated in vitro utilizing the MDBK cell line and the cytopathic inhibition assay. By using the microculture tetrazolium assay (also known as MTT) assay, the MDBK cell line was identified. (24)

Anti-Hypertensive Activity:

Mitragyna Parvifolia root alcohol extract's antihypertensive and vasorelaxant properties. After uninephrotectomy, an 11% w/v NACL solutions was administered with drinking water, and S. C. received a deoxy corticosterone acetate injection (20 mg/kg), which caused hypertension. Doses of 200 and 400 milligrams per kilogram of the M. P. root alcohol extract were administered. Serum levels of TG and TC were examined, as well as heart rate and systolic blood pressure. The isolated thoracic aorta was used to test the extract's vasorelaxation ability against contractions caused by calcium chloride on isolated tissue. (25)

Antiarthritic and Antipyretic Activity:

Acetic acid-induced arterial permeability in rats and Freund's adjuvant-induced arthritis in rats were used to test the antiarthritic properties of the methanolic extract, M. P. (MEMP) leaves, while yeast-induced pyrexia in rats was used to test the antipyretic properties. When taken orally at doses of 125, 250, and 500 mg/kg, MEMP had a strong antipyretic and antiarthritic effect. (11)

Antiproliferative and Antioxidant Activity:

The total phenolic and flavonoid contents, antioxidant capacity, lipid peroxidation, and antiproliferative activity on HeLa cell lines of bark and leaves of Mitragyna- Parvifolia (Roxb.) Korth were assessed. The aluminium chloride technique and the DPPH method for radical scavenging were used to estimate flavonoids and antioxidant potential, respectively. Giemsa or Acridine orange staining were used to examine cell morphology after TBARS and MTT assays revealed further lipid peroxidation & an antiproliferative impact. (26)

Anxiolytic Activity:

Several preparations of Mitragyna Parvifolia stem bark were tested for their anxiolytic properties in mice utilizing the marble burying tests (MBT) and elevated plus maze (EPM). The fraction that was rich in alkaloids had stronger anxiolytic effects. GAB allergic systems (VIII) C mediated the anxiolytic effects. MC is used as a moderate anxiolytic and to treat skin, infections, fever, and pain. (27)

Anticancer Activity:

Dichloromethane, an extract from Mitragyna Parvifolia tree stem bark has anticancer potential according to molecular docking studies and the MTTT assay. MCFT A549 & Hep G2 lines of cells were subjected to the MTT assay. The corresponding IC50 values were 402.8 µg/ml, 207.4 µg/ml, & 104.4 µg/ml. By using GC-MS analysis, the extract's phytoconstituents were identified. The NTST library was used to identify and name the most likely structures. By selecting the appropriate anticancer medication that targets VEGFR2, Kinases (lung cancer), (breast cancer), & EGFR Kinase (liver cancer) utilizing autodockivina, a molecular docking investigation was carried out on the chosen molecule. The docking investigation revealed that the extract had exceptional anticancer efficacy since the binding energy & interactions of the steroidal derivatives

were similar to those of the standards (Erlotinib, Sorafenib, and SYR). [4]

TOXICOLOGICAL AND SAFETY PROFILE OF *MITRAGYNA PARVIFOLIA* (ROXB.) KORTH.:

Limited and biased toward short-term, rodent studies employing leaf or bark extracts are the published safety data. Strong sub-chronic, chronic, reproductive, & genotoxicity data are mostly lacking, despite the fact that some studies indicate "practically non-toxic" results in acute tests. Differentiate between M. parvifolia and M. speciosa (kratom); a large portion of the information on kratom's toxicity to humans is not directly relevant to M. parvifolia. [29]

Acute Toxicity Studies (LD_{50}):

Using a modified Lorke method, the mice's median lethal dosage (LD50) of Mitragyna parvifolia MeOH extract was ascertained. After a 24-hour fast, the mice were split into five-mouse groups of either sex at random. The mice at each test group received different oral dosages of MEMP in graded amounts. After being given unrestricted access to water and food, the test group mice were watched for indications of acute toxicity for seven days. It was noted how many deaths (induced by the MEMP) occurred throughout this time.[30,31]

Safe Dosage Range:

According to preclinical research, Mitragyna parvifolia has a wide range of medicinal uses. Doses of 100–500 mg/kg orally in mice have been shown to exhibit pharmacological actions, including anti-inflammatory, analgesic, antiulcer, & antidiabetic properties; they are deemed safe and efficacious for experimental use. [20] Methanolic extracts displayed with LD_{50} above 5000 milligrams per kilogram, suggesting a significant safety margin, but ethanolic extracts could be tolerated as much as 1500 mg/kg without any fatality, according to acute toxicity studies. [32] Additionally, ethanol-based bark extract was reported to be safe up to 2000 mg per kilogram for 8 weeks during administration without hazardous symptoms in a model of chronic diabetic rats. [33] These results demonstrate the experimentally successful dosages fall well within the tolerable range; nevertheless, the safe dosage range for humans is still unknown and needs more research due to the lack of comprehensive sub-chronic & human clinical investigations. [34]

Reported Adverse Effects:

According to recent research, at pharmacologically efficacious dosages, Mitragyna parvifolia is typically safe in laboratory animals with no significant side effects noted. Up to 2000 mg/kg of ethanol-based bark extract for eight weeks did not cause any notable behavioural, haematological, or biochemical changes in rodents in acute or sub chronic toxicity trials. Likewise, ethanolic & methanolic extracts demonstrated a broad margin of safety, including LD_{50} values more than 5000 mg/kg or no discernible toxic symptoms or fatalities. [35]

Though these effects have not been consistently documented in M. parvifolia specifically, there is worry that at very high doses or with prolonged use, mild sedation, and gastrointestinal disturbances may occur due to its chemical similarity to other Mitragyna species (like M. speciosa). Long-term safety is therefore questionable because thorough research on chronic toxicity or adverse responses in humans is still absent, despite the fact that the evidence currently available supports a favourable safety profile. [33]

CONCLUSION:

Ethnopharmacological traditions and contemporary pharmacological research both indicate the substantial therapeutic potential of Mitragyna parvifolia (Roxb.) Korth., a long prized medicinal herb. Numerous biological actions, such as antiulcer, antioxidant, anti-inflammatory, antibacterial, analgesic, antidiabetic, antihypertensive, or anticancer properties, are attributed to its vast array of bioactive chemicals, especially flavonoids, phenolics, and indolic and oxindolic alkaloids. According to preclinical research, the plant extracts have a wide margin of safety and are generally safe at therapeutic dosages. Human clinical trials, reproductive safety evaluations, and thorough chronic toxicity investigations are still missing, nonetheless.

M. parvifolia is a good option for the creation of standardized phytomedicines, particularly in the treatment of gastrointestinal conditions like ulcers, according to this review. Its broader applicability requires bridging the divide between conventional wisdom and contemporary scientific validation. To determine its efficacy, safety, or standardized dosing regimens, future research should concentrate on thorough mechanistic studies, long-term security assessments, and well-planned clinical trials. With these developments, M. parvifolia has the potential to make a substantial contribution to next-generation drug discovery and evidence-based herbal treatments.

Future Perspectives

The therapeutic potential of M. parvifolia is highlighted by current research, but future studies should concentrate on:

- **Mechanistic insights:** thorough pharmacodynamic and molecular research to elucidate the mechanisms underlying its antioxidant, anti-inflammatory, and antiulcer properties.
- **Standardization:** Key bioactive indicators are isolated and quantified to guarantee consistency and repeatability in herbal compositions.
- **Toxicological profiling:** To determine long-term safety, thorough sub-chronic, chronic, or reproductive toxicity studies are required.
- **Clinical studies:** well-planned human trials to confirm safety, dose, and effectiveness.
- **Drug development:** investigation of innovative delivery methods and synergistic combinations to improve bioavailability and medicinal effect.

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