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PHYTOMEDICINE: A NEW FIELD TO TREAT DISEASES

Aakash Bhatnagar[1], Aqsa Shamsi[1], Mohd.Adil Tahseen[2], Anurag Pathak[3], Anjali Gangwar[3]

[1] B.Pharm, Mohammad Ali Jauhar University, Rampur, Uttar Pradesh

[2] PhD Research Scholar, Shobit University, Saharanpur, Uttar Pradesh

[3] Assistant Professor, S.R. Institute of Pharmacy, Bareilly, Uttar Pradesh

ABSTRACT

After receiving an unsatisfactory reaction to drugs, people in the West are increasingly turning to phytomedicine as a significant alternative therapeutic option. In fact, patients who reside in Eastern nations with a long history of traditional medicine frequently use herbal drug prescriptions, as the majority of the population finds it difficult to acquire Western medications. The effectiveness and potential adverse effects of herbal treatments have long been a source of debate among clinicians in the West. Except for Allopathy, all of India's officially recognized health systems—Ayurveda, Yoga, Unani, Siddha, Homeopathy, and Naturopathy—include a significant portion of herbal medications. Numerous Institutes/Universities have conducted extensive basic and clinical research using cutting-edge techniques on medicinal plants and their formulations. Therefore, information on the scientific basis of these plants will hopefully contribute to a greater understanding of Ayurveda and Indian herbal remedies worldwide.

Key Words: Phytomedicine, Traditional Medicine, Ayurveda, Unani, herbal remedies, formulations

INTRODUCTION

Phytomedicine derived from herbal sources is in high demand in the industrialized world due to its ability to heal a wide range of infectious disorders. Natural medicine is gaining increasing interest from both practical and scientific perspectives; however, the mechanism of action of traditional herbal remedies and similar natural items is much more complex than the mechanistic elucidation of a single bioactive ingredient. Because of their safety and lack of adverse effects, they have demonstrated their efficacy in basic health care. They also provide treatments for age-related illnesses such as memory loss, osteoporosis, immunological problems, etc. The newfound popularity is owing to their nearly miraculous success with cases that allopathic doctors had written off as hopeless, as well as their side-effect-free therapy. The integration of phytomedicine into the health system should be designed in such a way that there is no conflict between traditional and contemporary healthcare systems. (1)

The Indian subcontinent has a huge storehouse of medicinal plants utilized in traditional medical treatments, which also serves as a rich source of information. Several plant species are used to cure various ailments in indigenous systems such as Siddha, Ayurveda, Unani, and Allopathy. Around 20,000 medicinal plant species have been reported in India, however over 500 traditional groups employ roughly 800 plant species to treat various ailments. Because it has no side effects, plant-derived medicine is used as the first line of primary health care for 80% of the world's population. Finally, instead of using plants harvested in the wild, the trend toward domestication, biotechnological studies, and genetic improvement of medicinal plants will provide significant benefits, as it will be possible to obtain uniform and high-quality raw materials, which are critical to the efficacy and safety of herbal drugs. (2)

Phytochemicals are plant-based bioactive molecules that plants manufacture to defend themselves. Carotenoids, polyphenols, isoprenoids, phytosterols, saponins, dietary fibers, and specific polysaccharides are some of the important phytochemicals. These phytochemicals are powerful antioxidants with antibacterial, antidiarrheal, anthelmintic, antiallergic, antispasmodic, and antiviral properties. They also aid in gene transcription regulation, gap junction communication, immunity, and protection against lung and prostate cancer. The increased emphasis on translational research has broadened the scope of functional meals. (3)

ALKALOIDS AS THERAPEUTIC COMPOUND FROM PLANTS

Alkaloids constitute important secondary metabolites known to have medicinal activities. The chemicals have been divided into several groups based on their biosynthetic precursor and heterocyclic ring system, including indole, piperidine, tropane, purine, pyrrolizidine, imidazole, quinolozidine, isoquinoline, and pyrrolidine alkaloids. Alkaloids can prevent the beginning of numerous degenerative illnesses by scavenging free radicals or interacting with the oxidative reaction catalyst. Several research have been conducted to evaluate alkaloids from various plants for their diverse spectrum of medicinal actions. (4)

ROLE OF ALKALOIDS IN NEURODEGENERATIVE DISORDERS (5)

Class of alkaloids	**Alkaloids**	**Plants source**	**Diseases**
Isoquinoline alkaloids	Berberine	*Hydrastis canadensis* *Coptis chinensis* *Berberis vulgaris* *Berberis aristata*	Alzheimer's disease Parkinson's disease Huntington disease Epilepsy
	Salsoline	*Salsola oppositefolia*	Alzheimer's disease
	Galantamine	*Galanthus nivalis* *Leucojum aestivum*	Alzheimer's disease
Indole alkaloids	Geissospermine	*Geissospermum vellosii*	Alzheimer's disease
Pyrroloindole alkaloids	Physostigmine	*Physostigma venosum*	Alzheimer's disease Parkinson's disease
Piperidine alkaloids	Piperine	*Piper nigrum* *Piper longum*	Alzheimer's disease Parkinson's disease

			Epilepsy
Aporphine alkaloids	*Nantenine*	fruit of *Nandina domestica*	Epilepsy
Pyridine alkaloids	Nicotine	*Nicotiana tobaccum*	Alzheimer's disease
	Arecoline	*Areca catechu nut*	Schizophrenia
Methylxanthine derivatives	Caffeine	*Coffea arabica*	Alzheimer's disease Parkinson's disease
Lycopodium alkaloid	Huperzine A	*Huperzia serrate*	Alzheimer's disease
Indole β-carboline	Harmine	*Peganum harmala*	Alzheimer's disease

ALKALOIDS: THERAPEUTIC POTENTIAL AGAINST HUMAN CORONAVIRUSES

Alkaloids have been reported to be broad-spectrum coronavirus inhibitors in both animals and humans. While the methods by which HHT, oxysophoridine and tylophorine, and tylophorine analogs limit CoV replication are unknown, lycorine affects host factors to disrupt viral replication. Tetrandrine, fangchinoline, and cepharanthine, on the other hand, reduce TGEV replication by blocking virus translocation through the endolysosomal system and acting in tandem with a JAK-family inhibitor for comprehensive anti-CoV efficacy. (6)

EXAMPLES OF ALKALOIDS ACTIVE AGAINST CORONAVIRUSES. (6)

Alkaloid	**Coronavirus**	**Main Finding**
Homoharringtonine (HHT)	SARS-CoV-2	EC_{50} 2.10 μM (reduction in viral copy number) EC_{50} 2.55 μM (reduction in infectious virus)
	MHV, BCoV-L9 and HECoV-4408	Inhibits viral replication IC_{50} 11 nM
	PEDV	IC_{50} 0.112 μM in Vero E6 cells Decreases viral RNA levels in vivo in piglets Specific blockage of viral replication
Lycorine	SARS-CoV	IC_{50} 15.7 nM
Oxysophoridine	SARS-CoV-2	EC_{50} 0.18 μM and CC_{50} > 40 μM
Tetrandrine, Fangchinoline, and Cepharanthine	MERS-CoV HCoV-OC43	Block MERS-pseudovirus translocation through the endolysosomal system Inhibited HCoV-OC43-induced cell death in the early stage of infection and reduced

		virus replication by suppressing the expression of viral S and N proteins.
Tylophorine and Tylophorine analogs	SARS-CoV, MHV, and TGEV SARS-CoV, MERS-CoV, and TGEV	Anti-CoV replication activity; blocks virus-induced apoptosis and subsequent cytopathic effect in cells in vitro EC_{50} values for the natural and synthetic tylophorine compounds 8 to 1468 nM and 5 to 340 nM in ST and Vero 76 cells, respectively Targets viral RNA, thereby inhibiting TGEV replication Acts jointly with JAK family inhibitor for comprehensive anti-CoV
Indigo	SARS-CoV	Inhibits the cleavage activities of the 3CLpro IC_{50} values for cell-free and cell-based assays of 300 μM and 752 μM, respectively
Tryptanthrin and Indigodole B	HCoV-NL63	Reduces viral yield: tryptanthrin (IC_{50} 1.52 μM); indigodole B (2.60 μM) Virucidal activity: tryptanthrin (IC_{50} = 0.06 μM); indigodole B (IC_{50} = 2.09 μM) Tryptanthrin blocks viral RNA genome synthesis and the activity of the papain-like protease 2

ALKALOIDS WITH ANTI-INFLAMMATORY ACTIVITY.

The most researched classes for anti-inflammatory action were isoquinoline, quinoline, and indole alkaloids. Berberine was the most researched isoquinoline, active in practically all of the experimental paradigms. This chemical is found in *Berberis* and *Coptis*. It has a number of pharmacologic actions, including the suppression of TPA-induced mouse ear edema, indicating that this alkaloid may have anti-inflammatory potential. Warifteine, a bisbenzylisoquinoline alkaloid isolated from Cissampelos sympodialis, was found to inhibit eosinophil recruitment, eotaxin and cisteinyl leukotriene production in the pleural cavities and lungs of allergic mice, as well as the production of nitric oxide mediators. These findings emphasize warifteine potential as an anti-allergic and anti-inflammatory agent. (7)

ALKALOIDS WITH ANTI-INFLAMMATORY ACTIVITY. (7)

Substance and (Source)	Assay	Organism tested	Dose
Acanthine, oxy (*Berberis crataegina*)	In vivo, 5-HT-Induced pedal edema	Mouse	200 mg/Kg
Ailanthamide (*Zanthoxylum ailanthoides*)	In vivo, inhibitory activity on superoxide generation by human neutrophils	Human	$IC_{50} \leq 5.34$ µg/mL
Akuammigine, pseudo (*Picralima nitida*)	In vivo, carrageenan-induced pedal edema	Rat	1 mg/Kg
Ligustrazine (*Ligusticum chuanxiong*)	In vitro, macrophages	Human adult	400 mg/L
	In vivo, Cotton pellet granuloma	Mouse	50 mg/Kg
Amide, (2E,4E)-N-isobutyl-6-oxohepta2,4-dien (*Zanthoxylum ailanthoides*)	In vivo, inhibitory activity on superoxide generation by human neutrophils	Human	$IC_{50} \leq 5.34$ µg/mL
Brucine (*Strychnos nux-vomica*)	In vivo, carrageenan-induced pedal edema	Rat	15 mg/Kg
Caulerpin (*Caulerpa racemosa*)	In vivo, capsaicin-induced ear edema	Mouse	100 µmol/Kg
Colchicine (*Colchicum autumnale*)	In humans	Human adult	oral 0.5 mg/ person
Evolitrine (*Evodia lunuankeda*)	In vivo, carrageenan-induced rat paw edema	Rat	20 mg/Kg
Persicaside (*Prunus persica*)	In vitro, inhibitory activity on NO production	Rat	40 µg/mL
	In vitro, inhibitory activity on PGE2 production	Rat	40 µg/mL

ALKALOIDS FOR DIABETES MANAGEMENT

Metformin, one of the most extensively used diabetes medications, developed from *Galegine officinalis* is widely used in the treatment of type 2 diabetes. Similarly, anti-diabetic phytochemicals such as flavonoids such as quercetin, alkaloids such as berberine, terpenes such as thymoquinone, and phenylpropanoids such as chlorogenic acid are employed. These phytochemicals have comparable modes of action, which are mediated via DPPH-4 activity by reducing α-glucosidase enzyme activity, inhibiting α-amylase, and enhancing glucose absorption by the body's adipose and muscle cells. These phytochemicals have shown encouraging results in a

variety of in vitro and in vivo investigations; however, because of the scarcity of data on the toxicity profile of these components, additional research into risk-benefit ratios is required.

ALKALOIDAL PHYTOCONSTITUENTS USED FOR THE MANAGEMENT OF DIABETES MELLITUS

Phytoconstituent (Alkaloids)	**Mechanism of action**
Avarol *Dysidea avara*	Inhibition of α-glucosidase enzyme can help in delaying the digestion of carbohydrates, thereby reducing the levels of glucose in the blood IC_{50} value for various avarol derivatives: 0.05–0.12 mM
Berberine *Berberis* *Tinospora cordifolia*	Berberine is known as an AMP-activated protein kinase (AMPK) activator. Its insulin-independent hypoglycemic effect is related to the inhibition of mitochondrial function, stimulation of glycolysis, and activation of the AMPK pathway, which inhibits alpha-glucosidase. IC_{50} value: 0.68 μM
Casuarine 6-o-a-glucoside *Syzygium malaccense*	It acts by stimulating insulin secretion, inhibiting intestinal α-amylase activity, and increasing muscle basal glucose uptake along with antioxidant activity. IC_{50} value of casuarine compounds: 9.7 μM
Catharanthine, Vindoline, and Vindolinine *Catharanthus roseus*	Vindoline exhibits an insulinotropic effect by enhancing glucose-stimulated insulin secretion (GSIS). It was also found to increase plasma insulin in STZ-induced diabetic rats. In a recent study, vindoline reduced the voltage-dependent outward potassium currents through Kv2.1 inhibition. The combined effects resulted in fasting plasma glucose, improved oral glucose tolerance, and lowered serum glycated hemoglobin (HbA1c) and triglyceride (TG) levels. IC_{50} values: 59.6 μM, >30 μM, and >50 μg/mL, respectively.
Calystegine B2 *Nicandra physalodes*	In an in vitro study, calystegine B2 inhibited mainly sucrose activity by β-glucosidase alpha inhibitor and intestinal glucose absorption IC_{50} value: range 4.6 μM
Harmane, Norharmane, Pinoline *Tribulus terrestris*	Stimulatory action on insulin secretion by the activation of imidazoline-I binding sites in the pancreatic cell. IC_{50} values: 5 μM; 51–58 μM and 0.11 μM

Jambosine *Syzygium cumini*	Reduces free radicals, improves the functioning of beta-pancreatic cells, and upregulates the PPARγ and PPARα. IC_{50} value: 2.5 nM
Jatrorrhizine, Magnoflorine, Palmatine, Tembetarine *Tinospora cordifolia*	Lowering of blood glucose, increase in insulin sensitivity, inhibition of a-amylase and a-glucosidase activities, direct effect on carbohydrate metabolism IC_{50} value (derivatives): ~1.05 μM
Lepidine and semilepidine *Lepidium sativum*	Reduction in oxidative damage and modulation of antioxidant enzymes, potentiation of pancreatic secretion of insulin from the remaining islet β cells IC_{50} value: 1.42 ± 0.04 mg/mL
Mahanimbine *Murraya koenigii*	Inhibits alpha-amylase and alpha-glucosidase IC_{50} value: ranges from 3.5 to 64 μM
Swerchirin *Swertia chirayita*	Lowers blood glucose level by stimulating insulin release from islets of Langerhans IC_{50} value: 20 μM

ALKALOIDS AS ANTICANCER AGENTS

Alkaloids show strong antitumor efficacy against a variety of malignancies. They are a chemically heterogeneous group of approximately 2500 basic nitrogen containing substances, found in about 15 percent of all vascular land plants and in more than 150 plant families, widely distributed in higher plants particularly the dicotyledons (in abundance in the families Apocynaceae, Papaveraceae, Papilionaceae, Ranunculaceae, Rubiaceae, Rutaceae and Solanaceae), but less frequently in lower plants and fungi. *Catharanthus roseus* (Apocynaceae) heralded a new era in anticancer drug development with the isolation of the first important anticancer alkaloid, vinblastine and vincristine.

Vinblastine and vincristine are generally used in conjunction with other cancer chemotherapeutic medications to treat a range of malignancies, including leukemias, lymphomas, advanced testicular cancer, breast and lung cancer, and Kaposi's sarcoma.

Camptothecin, which was isolated from *Camptotheca acuminata* (Nyssaceae), has anticancer action in vitro and in animals. Topotecan and irinotecan are semi-synthetic derivatives of camptothecin that are used to treat ovarian and small-cell lung tumors, as well as colorectal malignancies. Naucleaorals A and B were discovered to be a pair of novel isomeric indole alkaloids isolated from the roots of *Nauclea orientalis*. It causes cytotoxicity in HeLa and KB cells.

Liriodenine, an isoquinoline alkaloid derived from *Cananga odorata* (Annonaceae) has powerful cytotoxic, antiproliferative, and apoptosis-inducing actions on human lung cancer cells. It was discovered to be a strong inhibitor of topoisomerase II both in vivo and in vitro. Clivorine, a pyrrolizidine alkaloid derived from *Ligularia hodgsonii* has antiproliferative action in human normal liver L-02 cells via inducing apoptosis. Harmina harmane, harmaline, harmalol, and tryptoline, beta carboline alkaloids derived from *Peganum harmala* showed

anticancer action by blocking DNA topoisomerases and interfering with DNA synthesis. It was the most active molecule, with specific efficacy against lung (GI_{50} = 0.06 μM), ovarian, and renal cell lines.

Punarnavine, an alkaloid derived from the plant *Boerhaavia diffusa* has antimetastatic action in B16F-10 melanoma cells in C57BL/6 mice. It was found to be effective in inhibiting the metastatic development of B16F-10 melanoma cells in mice. *Arisarum vulgarae* contains the alkaloid bgugaine. In the HepG2 cell line, it causes DNA damage. Stemona alkaloids were isolated from the roots of *Stemona aphylla* and *S. burkillii*. They have a significant function as a (P-glycoprotein) modulator in vitro and may be useful in the treatment of multidrug-resistant malignancies. (9)

PHENOLIC COMPOUNDS FROM PLANTS AS PHYTOMEDICINE

Phenolic compounds are a large class of plant secondary metabolites that are widely distributed in higher plant organs such as vegetables, fruits, spices, grains, legumes, and nuts6, and play important roles in a variety of physiological processes such as plant quality, coloring, flavor, and stress resistance. The inherent antioxidant, antibacterial, anticarcinogenic, and anti-inflammatory effects of phenolic compounds have recently been a focus of research and application. Flavonoids, phenolic acids, tannins, stilbenes, and lignans are the primary families of phenolic compounds, and they all have a similar chemical structure that consists of an aromatic ring with one or more hydroxyl substituents.

Multiple biological effects of phenolic compounds against various illnesses and disorders have received considerable attention in recent years. Such compounds have anticarcinogenic, antithrombotic, antiulcer, antiartherogenic, antiallergenic, anti-inflammatory, antioxidant, immune-modulating, antibacterial, cardioprotective, and analgesic properties. Numerous research studies have been conducted to identify possible active substances as well as to investigate the underlying processes for avoiding and even correcting disease damage. However, further study is needed to understand the mechanisms of action of these active phenolic compounds, as well as their in vivo effects, bioavailability, and efficacy.

Delphinidin has the ability to inhibit cell growth and promote caspase-mediated apoptosis, resulting in tumor size reduction, as demonstrated by in-vitro human cell lines and in-vivo murine model assays, 7-hydroxymatairesinol has the ability to inhibit tumor growth and stop tumor cell proliferation, as demonstrated by in-vivo murine models assay. Caffeic acid inhibited tumor cell growth in the LNCap cell lines experiment, but Ferulic acid inhibited tumor size in the PC-3 cell lines assay, inevitably leading to apoptosis.

Cyanidin-3-rutinoside and cyanidin-3-glucoside have demonstrated dose-dependent tumor inhibitory impact in in-vitro human cell lines assay, p-coumaric acid has shown tumor inhibitory action in A549 assay, and Quercetin in PEG 400 liposomes has Tumor inhibitory activity that leads to apoptosis has been observed in in-vivo mouse models. Cinnamic acid inhibited tumor development in the HT-29 cell line experiment. Gallic acid has been shown to reduce tumor size in the MDA-MB-231 cell line experiment, while Caffeic acid has been shown to suppress tumor development and induce apoptosis in the MDA-HB-231 assay.

Dicoumarol can improve the drug's anticancer efficacy, as revealed by an in-vitro human cell line assay using the MDA-HB-231 assay. Protocatechuic acid and ferulic acid can inhibit MMP and slow tumor cell development. Cinnamic acid derivatives, such as CAA and CAPE, can block MMP-9 and MMP-2 activities, preventing hepatoma cell proliferation and metastasis. As a result, phenolic derivatives with MMP inhibitory

properties can prevent malignant cells from spreading metastatically. Polyphenolic substances, such as Ellagic acid (EA), can reduce Bcl-2 expression in breast cancer while increasing p21 levels via phosphatidylinositol-3, 4, 5-triphosphate-3-phosphatase, resulting in tumor death. Flavonoids can also cause biomolecular damage in vitro via peroxynitrite, block carcinogenic metabolite activation, cell-cycle arrest by apoptosis, and limit proliferation and angiogenesis. Apigenin reduces cell adhesion and invasion, lowers diolepoxide 2 forms, inhibits mitochondrial proton F0F1-AT Pase/ ATP synthesis, inhibits prostaglandin and IL-6, 8 productions, and suppresses the expression of intercellular adhesion molecule-1 (ICAM-1). Antimutagenic and anti-angiogenesis properties have been demonstrated for genistein, luteolin, quercetin, and silymarin.[10-11]

Polyphenols have antibacterial action against a wide range of microorganisms. Among polyphenols, flavanols, flavonols, and phenolic acids have the highest antibacterial activity due to their ability to inhibit bacterial virulence factors such as enzymes and toxins, interact with the cytoplasmic membrane, suppress biofilm formation, and work in tandem with antibiotics. The time-kill test or MBC (minimal bactericidal concentration) tests revealed that substances such as epigallocatechin gallate, galangin, and 3-O-octanoyl-(+)-catechin promoted bacterial cell eradication in MRSA-YK, *S. aureus* NCTC 6571, and EMRSA-16 strains. 3-O-octanoyl- (-)-epicatechin, on the other hand, causes pseudo multicellular aggregates to develop in both methicillin-resistant and susceptible *S. aureus* strains. A similar effect has been reported in the presence of epicatechin gallate, however, it is unclear whether real or pseudo multicellular aggregates were formed in the presence of flavonoids. The aggregates generated are thought to represent a single colony-forming unit (CFU), giving the erroneous appearance of a reduction in the number of CFUs. This sort of action clearly shows that flavonoids do not have bactericidal activity, but that aggregate formation is responsible for the lower number of CFUs.[12]

ANTISTAPHYLOCOCCAL PROPERTIES OF FLAVONOLS, FLAVANOLS AND PHENOLIC ACIDS.[12]

Phenolic Compound	**Examined Strains**	**Synergism with Antibiotics**
Galangin	*S. aureus* NCTC 6571	Penicillin G
Quercetin	MRSA clinical strains	Rifampicin Ciprofloxacin
Kaempferol	MRSA clinical strains	Rifampicin Ciprofloxacin Fluoroquinolone
(−)-Epigallocatechin gallate	MRSA and MSSA clinical and standard strains	Oxacillin Ampicillin/Sulbactam Penicillin Imipenem Panipenem Meropenem

		Tetracyclin Oxytetracycline
Epicatechin gallate	MRSA clinical strains	β-lactams Ampicillin Ampicillin/Sulbactam Cefazolin Cefepime Imipenem/Cilastatin
(+)-catechin	MRSA clinical strains	Ampicillin Ampicillin/Sulbactam Cefazolin Cefepime Imipenem/Cilastatin
Catechin hydrate	MRSA and MSSA clinical and standard strains	Clindamycin Erythromycin
Protocatechuic acid ethyl ester	MRSA and MSSA clinical and standard strains	Clindamycin
Caffeic acid	MRSA and MSSA clinical and standard strains	Clindamycin Erythromycin Cefoxitin

.BIOACTIVE CONSTITUENTS OF ESSENTIAL OILS

Terpenes, also known as isoprenoids, are the most abundant and diverse category of naturally occurring substances found mostly in plants, while bigger groups of terpenes such as sterols and squalene can be found in animals. They are in charge of plant scent, flavor, and pigment. Terpenes and terpenoids are a grouping of isoprene units, which are naturally occurring, volatile, unsaturated 5-carbon cyclic chemicals that emit a perfume or flavor to protect themselves from creatures that feed on particular types of plants. Terpenes have several roles in plants, including thermoprotection, signaling activities, pigments, taste, and solvents, but they also have medical benefits.[13]

Several studies have demonstrated that certain terpenes could reduce inflammation symptoms by decreasing the release of pro-inflammatory cytokines. For example, the nuclear transcription factor-kappa B, interleukin 1, and the tumor necrosis factor-alpha. certain terpenes (D-Limonene, α-Phellandrene, Terpinolene, Borneol, Linalool, and triterpene glycosides) can lower the production of TNF-α, IL-1, and IL-6 in the Raw 264.7 macrophages cell line. Experiments utilizing in vivo models such as Swiss mice, Wistar rats, and albino mice (BALB/C) yielded similar results. [14]

Non-alcoholic fatty liver disease (NAFLD), a widespread metabolic illness globally, causes a health burden as well as economic issues. Terpenoids have been shown to effectively prevent and treat FALD by improving lipid metabolism, inhibiting oxidative stress, inhibiting inflammation, and preventing fibrosis. They help to treat

NAFLD by modulating lipid metabolism, insulin resistance, oxidative stress, and inflammation. Terpenoid therapy primarily targets the AMPK, PPARs, Nrf-2, and SIRT 1 pathways.[15]

DIFFERENT TYPES OF TERPENES AND THEIR PROPERTIES[13]

Classification	**Carbon atoms**	**Species produced from**	**Medicinal uses**
Monoterpenes	C_{10}	*Quercus ilex*	Fragrances, repellent
Sesquiterpenes	C_{15}	*Helianthus annuus*	Treat malaria, treat bacterial infections, and migraines
Diterpenes	C_{20}	*Euphorbia, salvia miltiorrhiza*	Anti-inflammatory, cardiovascular diseases
Triterpenes	C_{30}	*Centella asiatica*	Wound healing, increases circulation

TERPENES ADDED IN ANTI-INSECT FORMULATIONS[13]

Terpene type	**Function**
Limonene	This is strongly preferred. Limonene enhances the properties of other terpenes
Beta-ionone	Antibacterial and antifungal properties
Geraniol	Similar level activity like beta-ionone. Geraniol possesses antibacterial and antifungal properties.
Eugenol	This is also the active terpene in clove oil. This possesses anesthetic properties which help with the itching that comes with bug bites. Also, contain antibacterial and antifungal properties
Myrcene	Possesses antifungal, antibacterial properties

THE EFFECTS AND MECHANISMS OF TERPENOIDS ON NAFLD[14]

Compound	**Animal/Cell Model**	**Dosage (mg/kg/d; μM/24 h)**	**Target/Pathways/Mechanism**	**Effects**
Paeoniflorin	HFD-induced NAFLD mice	0.05% in diet	Activation of the CD36/AMPK signaling pathway	Reduced body weight, improved insulin resistance, anti-inflammatory, inhibition of lipid accumulation, attenuated hepatic adipose infiltration
	Fructose-induced	10, 20, 40	Activation of the AMPK signaling pathway	Inhibition of hepatic lipid accumulation, improved

	metabolic syndrome rats			insulin resistance, inhibition of hepatic steatosis, inhibition of hepatic lipogenesis, promotion of fatty acid oxidation
	HFD-induced NAFLD rats	20, 60, 100	Inhibition of the ROCK/NF-κB signaling pathway	Anti-inflammatory, ameliorated hepatic steatosis, reduced lipids
Geniposide	(PA + OA)-induced HepG2 cells	0, 65, 130, 260, 390, 520 μmol/L/24 h	Upregulation of the Nrf2/AMPK/mTOR signaling pathways	Inhibition of lipid accumulation, anti-oxidative stress, anti-inflammatory
	HFD-induced NAFLD rats	25, 50, 100	Increased expression of PPARa gene	Ameliorated hepatic steatosis, anti-oxidative stress
Genipin	HFD-induced NAFLD mice; (PA + OA)-induced cells primary hepatocytes of mice	5, 20; 5, 20	Regulation of the miR-142a-5p/SREBP-1c axis	Reduced body weight gain, increased locomotor activity, improved insulin resistance, alleviated hyperlipidemia, inhibition of lipid accumulation
	HFD-induced NAFLD mice	5, 20	Suppressed UCP2	Reversed liver damage, anti-pyroptosis
Sweroside	HFD-induced NAFLD mice	60, 120, 240	Increases expression of PPARa gene	Reduced body weight, improved insulin resistance, inhibited hepatic steatosis, anti-inflammatory
Swertiamarin	HFD-induced NAFLD mice; LPSO-induced murine	10, 100; 1, 10, 50	Suppressed activation of the p38 MAPK and NF-κB signaling pathways	Ameliorated hepatic steatosis, anti-inflammatory, reduced body weight, improved insulin resistance

	monocytic cells			
Aucubin	Tyloxapol-induced NAFLD mice	10, 20, 40	Activation of the Nrf2/HO-1 and AMPK signaling pathways	Inhibition of lipid accumulation, anti-oxidative stress, anti-inflammatory
Gentiopicroside	Tyloxapol-induced NAFLD mice; (PA + OA)-induced HepG2 cells	20, 40, 80; 0, 4, 20, 100, 200, 500	Upregulation of the Nrf2 signaling pathway	Inhibition of hepatic lipid accumulation, anti-oxidative stress
Curcumol	HFD-induced NAFLD mice	15, 30, 60	Regulation of the YAP/NCOA4 signaling pathway	Inhibition of hepatocyte senescence, suppressed ferritinophagy
	HFD-induced NAFLD rats	25, 50, 100	Regulation of the TLR4, TAK1, and NF-κB/P65 signaling pathways	Anti-inflammatory, improved liver function, anti-fibrosis, anti-apoptosis
β-patchoulene	HFD-induced NAFLD rats; (FFA + PA + OA)-induced HepG2 cells	10, 20, 40; 40	Activation of the AMPK signaling pathway	Inhibition of hepatic lipid accumulation, improved insulin resistance, ameliorated hepatic steatosis, inhibition of hepatic lipogenesis, promotion of fatty acid oxidation
	HFD-induced NAFLD rats	10, 20, 40	Activation of the CD36/AMPK signaling pathway	Reduced body weight, reversed liver damage, ameliorated hepatic steatosis, anti-oxidative stress, anti-inflammatory
β-caryophyllene	PA-induced HepG2 cells	40	Activation o the f AMPK signaling pathway	Inhibition of hepatic lipid accumulation
Ginkgolide B	HFD-induced NAFLD mice	0.1 % in diet	Activation of pregnane X receptor	Reduced body weight, ameliorated hepatic steatosis

	HFD-induced NAFLD mice; (PA + OA)-induced HepG2 cells	20, 30; 4, 8, 16	Increased Nrf2 expression	Anti-oxidative stress, reduced body weight, inhibition of lipid accumulation, anti-inflammatory
Acanthoic acid	Modified Lieber–DeCarli diet-induced mice	20, 40	Via FXR–LXR axis	Inhibition of hepatic lipid accumulation, anti-fibrosis, regulation of fatty acid synthesis
Dehydroabietic acid	HFD-induced NAFLD mice; OA-induced HL7702 cells	10, 20; 2.5, 5, 10	Activation of the Keap1/Nrf2-ARE signaling pathway	Reduced blood lipid, inhibition of ferroptosis
Ginsenoside Rg1	(PA + OA)-induced HepG2 cells	25, 50	Regulation of PPAR α and PPAR γ expression	Inhibition of lipid accumulation, ameliorated hepatic steatosis
	D-galactose-induced fatty liver disease mice	40	Upregulation of FOXO1 gene	Anti-inflammatory, inhibition of lipid accumulation
Ginsenoside Rg2	HFD-induced NAFLD mice	2.5, 5, 10	Regulation of the SIRT1 signaling pathways	Improvement of lipid and glucose disorders, anti-oxidative stress, anti-apoptosis, inhibition of lipid accumulation
Ginsenoside Rb1	HFD-induced NAFLD mice	10	Activation of PPAR-γ expression	Reduced body weight, improved glucose metabolism, inhibition of lipid accumulation, anti-apoptosis
Ginsenoside Rb2	db/db mice, OA-induced HepG2 cells	10; pretreated with 0.1, 1, 10, 50,	Regulation of the SIRT1 and AMPK signaling pathways	Alleviated hepatic steatosis, improved glucose tolerance, regulation of hepatic

		100 μmol/L/4h		autophagy, inhibition of lipid accumulation
Ursolic acid	HFD-induced NAFLD rats; human normally hepatic immortal cell line HL-7702	0.125, 0.25, 0.5% in diet; 0, 25, 50, 100	Regulation of PPAR α expression	Reduced body weight, alleviated hepatic steatosis, improved metabolic disorders, improved insulin resistance, anti-inflammatory, anti-oxidative stress
Betulinic acid	HFD-induced NAFLD rats	0.1% in diet	Regulation of the PERK/EIF2α/ATF4/CHOP signaling pathway	Enhanced energy expenditure, modulation of bile acids, alleviated hepatic steatosis, anti-inflammatory, alleviated ER stress
	HFD-induced NAFLD mice; (PA + OA)-induced mice primary hepatocytes	150; 10	Inhibition of the YY1/FAS signaling pathway	Inhibition of lipid accumulation, alleviated fatty acid synthesis, anti-fibrosis, anti-inflammatory, inhibition of excessive lipogenesis
Oleanolic acid	HFD-induced NAFLD rats	25, 50, 100	Inhibition of LXRs, activation of the AMPK pathways	Alleviated hepatic steatosis, anti-inflammatory, anti-oxidative stress, improved insulin resistance
Astragaloside IV	(PA + OA)-induced HepG2 cells and primary murine hepatocytes	50–200	Activation of the AMPK signaling pathway	Inhibition of lipid accumulation, inhibition of lipogenesis, alleviated ER stress
	High-concentration insulin or	25.6, 51.2, 102.4	Inhibition of protein tyrosine phosphatase 1B	Improved insulin resistance, inhibition of lipid accumulation

	OA-induced HepG2 cells			
Mogroside V	HFD-induced NAFLD mice	400, 800	Upregulation of pAMPK expression	Inhibition of lipid accumulation, anti-inflammatory, anti-oxidative stress
	HFD-induced NAFLD mice; (PA + OA)-induced human LO2 cells	25, 50, 100; 15, 30, 60,120	Activation of the AMPK signaling pathway	Inhibition of lipid accumulation, ameliorated hepatic steatosis
Asiatic acid	HFD-induced NAFLD rats	4, 8	Inhibition of the ERS signaling pathway	Inhibition of lipid accumulation, anti-inflammatory, anti-oxidative stress
Corosolic acid	HFD + CCl4-induced NAFLD mice; FFA + OA + PA-induced HepG2 cells	10, 20; 5, 10, 20	Regulation of the TGF-β1/Smad2, NF-κB, and AMPK signaling pathways	Inhibition of lipid accumulation, anti-inflammatory, anti-fibrosis
Arjunolic acid	HFD-induced NAFLD rats; (PA + OA)-induced HepG2 cells	100, 200; 12.5, 50	Upregulation of PPAR-γ expression	Inhibition of lipid accumulation, ameliorated hepatic steatosis, reduced blood lipids
Ganoderic acid A	HFD-induced NAFLD rats	20, 40	Activation of the AMPK signaling pathway	Inhibition of lipid accumulation, anti-inflammatory, reduced live weight
Rotundic acid	HFD-induced NAFLD rats; insulin-induced primary hepatocytes	10, 30, 100; 6.25–200	Downregulation of the SREBP-1c/SCD1 signaling pathway	Inhibition of lipid accumulation, improved dyslipidemia, protection against hepatic injury, anti-inflammatory,

				inhibition of excessive lipogenesis
Lycopene	HFD-induced NAFLD mice	100, 1000	Upregulation of PPARa-inducible genes	Ameliorated hepatic steatosis
	HFD-induced NAFLD rats	5, 10, 20	Downregulated expression of TNF-α and CYP2E1	Improved lipid profiles, reduced lipid peroxides, reduced blood lipids
	HFD-induced NAFLD mice	0.05% in diet	microRNA-21-induced downregulation of fatty-acid-binding protein 7	Ameliorated hepatic steatosis, inhibition of hepatic lipid accumulation
β-cryptoxanthin	HRCD + DKO-induced NAFLD mice	10	Activation of the SIRT1/AMPK signaling pathway	Inhibition of lipid accumulation, alleviated hepatic steatosis, increased cholesterol efflux
Lutein	HFD-induced NAFLD rats	0, 12.5, 25, 50	Activation of the SIRT1/PPAR-α signaling pathway	Reduced body weight, alleviated hepatic steatosis, improved insulin resistance

Bioactive terpenoids, their sources, and mechanisms of action in psychiatric disorders. (15)

Psychiatric Disorders	**Sources**	**Bioactive Terpenoids**	**Mechanisms of Action**
Autism Spectrum Disorder	*Salvia*	Diterpenes	Facilitate the activity of GABA transaminase
	Bacopa monniera	Bacosides A and Saponins A, B, C, and triterpenoid saponins	Decrease hippocampal serotonin levels
	Curcuma longa	Curcuminoids and co-occurring terpenoids	Decrease IL-6 level, suppresses the pro-inflammatory gene expression by blocking phosphorylation

	Piper nigrum Piper longum	Piperine alkaloids and terpenes	Reduced serotonin levels and oxidative parameters.
Schizophrenia	*P. vulgaris* var.lilacina	Oleanolic acid (plant-derived pentacyclic terpenoid)	Affected the metabolism of catecholamine and increased levels of 5-HT or NE due to MAO inhibition
	Panax ginseng	Ginsenosides (triterpene saponins)	Increased certain neurodevelopmental proteins
	Coniferous tree *Eucalyptus* oil, camphor oil, and *Opunita humifusa*	α-Pinene (monoterpene)	α-Pinene enhanced the function of the GABA-A receptor and played a vital role in GABAergic system
Attention-Deficit/Hyperactivity Disorder	*Radix preparata*	Catalpol (iridoids are derivatives of monoterpenes)	Upregulate several regulatory proteins (BDNF), cyclin-dependent kinase 5 (Cdk5), p35
Bipolar Disorder	*Centella asiatica*	Asiatic acid (Triterpenoid)	Asiatic acid could cross the blood–brain barrier and significantly restored oxidative stress marker
Major Depression Disorder	*Nigella sativa*	Monoterpenes, alkaloids, triterpenes, and saponins	Inhibiting the reuptake of norepinephrine, serotonin, and dopamine
	Boswellia serrata	Boswellic acids are the series of pentacyclic terpenoid molecules	*Boswellia serrata* showed high reducing ability of scavenging free

			radicals like NO, peroxide radical, O2., OH, DPPH (1,1-Diphenyl-2-picrylhydrazyl)
	Pimenta pseudocaryophyllus	Oleanolic acid	OA attenuated the depletion of indolamine and catecholamine
	Panax ginseng	Ginsenoside Rg1	Exerted positive effects on neurogenesis within the hippocampus and increased BDNF protein levels
Anxiety Disorder	*Centella asiatica*	ECa 233,triterpenoid glycosides including asiaticoside, madecassoside, asiatic acid and madecassic acid	Facilitated GABAergic mechanism
Sleeping disorder	*Valeriana wallichii*	Volatile oil (valerianic oil) containing valerenic acid, isovalerenicacid, and terpineol	Normalized monoamines neurotransmitters

CONCLUSION

Indigenous tribes and cultures, including those of Africa, India, and China, have used herbal treatments for thousands of years. Our apothecaries in the West were similarly stocked with therapeutic herbs and traditional treatments before we had synthetic medication. While many of the chemicals employed by our ancestors have been shown to have medicinal properties, some of the more bizarre remedies were unsubstantiated. Herbal remedies, in contrast, are typically kinder to the body. Natural remedies have fewer adverse effects when used at the prescribed dosages. Traditional medicine is all about holistic health and preserving the body's equilibrium, in contrast to many modern techniques that treat symptoms without addressing the underlying reasons. This implies that your alternative medicine doctor will make an effort to determine what your body is trying to tell you and then create a treatment plan that is tailored to your particular needs and physical condition.

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