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Alkaloids from *Piper:* A Review of its Phytochemistry and Pharmacology

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Abstract: *Objective:* Piper has been used for long timelike condiment and food, but also in traditional medicine around of the world. This work resumes the available and up to date work done on members of the Piperaceae family and their uses for therapeutic purposes. *Methods:* Information on Piper genus was gathered via internet using scientific databases such as Scirus, Google Scholar, CAB-abstracts, MedlinePlus, Pubmed, SciFinder, Scopus and Web of Science. *Results*: The large-leafed perennial plant *Piper* is used for its spicy aromatic scent and flavor. It has an important presence in the cuisine of different cultures. Another quality of these plants is their known medicinal properties. It has been used as emollient, anti-rheumatic, diuretic, stimulant, abortifacient, anti-inflammatory, antibacterial, antifungal and antidermatophytic. A survey of the literature shows that the genus *Piper* is mainly known for its alkaloids with cytotoxic, chemopreventive, anti-metastatic and antitumor properties in several types of cancer. Studies of its alkaloids highlight the existence of various potential leads to develop new anti-cancer agents. Modern pharmacology studies have demonstrated that its crude extracts and active compounds possess wide pharmacological activities, especially asantioxidant, anti-depressive, hepatoprotective, antimicrobial, anti-obesity, neuropharmacological, to treat cognitive disorders, anti-hyperlipidemic, anti-feedant, cardioactive, immuno-enhancing, and anti-inflamatory. All this evidence supporting its traditional uses. *Aim of the review*: This review summarizes the up-to-date and comprehensive information concerning the botany, traditional use, phytochemistry and pharmacology of Piper together with its toxicology, and discusses the possible trend and scope for further research on Piper in the future.

Keywords: *Piper*, Piperaceae, complementary medicine, phytochemical constituents, pharmacological actions.

1. INTRODUCTION

Traditional Medicine is still being used nowadays in all parts of the world and has been growing in economic importance particularly by the use of medicinal plants that have a respectable position today, especially in developing countries, where modern health services are limited and represent the only accessible treatment. According to the World Health Organization, the current estimative suggests that many developed countries have a big proportion of the population making use of some sort of traditional practice, especially the use of the medicinal plants. Although the access to the modern medicine is not the problem in these countries, the use of medicinal herbs has kept its popularity for historical and cultural reasons [1]. Medicinal plants represent an important health and economic component of biodiversity and conservation and sustainable use, according to Rhaman *et al.* [2]. Information of the traditional knowledge of medicinal plants and their uses would represent a vital role in the discovery of novel products from plants as chemotherapeutic agents [3]. Members of the *Piper* genus are of commercial, economical, and medicinal importance. Economically, the Piperaceae is employed for the production of pepper in worldwide spice markets. Plants from the genus *Piper* have been used for a number of practical applications, including as remedies in many traditional medicinal systems, such as traditional Chinese medicine, the Indian Ayurvedic system, and folklore medicines of Latin America and West Indies. *P. methysticum* has been shown to contain insect antifeedant activity. *P. amalago*, distributed from Mexico to Brazil, is used for several conditions, including gastrointestinal and chest pain. Phytochemical investigations of many *Piper* species have resulted in the isolation of numerous biologically active natural products including alkaloids, lignans, unsaturated amides, flavones, aristolactams, long and short chain esters, monoterpenes, sesquiterpenes, arylpropanoids, aldehydes, ketones, propenylphenols and chalcones. Amide alkaloids are typical constituents in the Piperaceae family, most of the compounds known being based on piperidine, pyrrolidine or isobutylamine [4]. Therefore, the genus Piper is known to contain molecules of therapeutic importance. In the last few decades, several studies have been carried out on these medicinal plants that also provide evidence in favor of their conventional uses. The purpose of this review is to provide comprehensive information on the botany, traditional uses, phytochemistry, pharmacological research and toxicology of

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Piper and to explore its therapeutic potential to evaluate future research opportunities.

2. BOTANY, TRADITIONAL USE AND FOOD PROPERTIES

The family Piperaceae, (Magnoliopsida, Magnoliidae, Piperales, Piperaceae) together with other members of the order Piperales such as the Aristolochiaceae, Saururaceae, and Lactoridaceae, has been classified among the basal Angiosperms. Biodiversity in the Neotropics is associated with a variety of biomes including dry highlands, flooded areas, and forest [5]. Within these tropical and subtropical regions, some 2000 species representing the fivemajor genera of the family Piperaceae, namely*Piper*, *Peperomia*, *Zippelia*, *Manekia*, and *Verhuellia* are to be found [6]. Species of Piper are located in all types of vegetation but mostly as components of pioneer vegetation. The greatestconcentrationof species is foundin the countries ofthe Andes. The most well known species are *Piper nigrum* L. (pepper) and *Piper methysticum* (kava).

The genus Piper is a member of the family Piperaceae also known as the pepper family, is a large family of flowering plants. The group contains roughly 3,610 currently accepted species in five genera. The earliest classifications of Piperaceae emphasizing *Piper* recognized between seven and 15 genera within the current circumscription of the genus. The vast majority of peppers can be found within the two main genera: Piper (1000 species) and Peperomia (1600 species). The genus *Piper* included 1000 species making one of the largest genera of basal angiosperms [7]. One view on the phylogenetic position of Piperaceae is among a diverse assemblage of dicots termed "paleoherbs" [8], plants that resemble monocots in certain vegetative features (e.g., adaxial prophyll, scattered vascular bundles). More recently, the Piperaceae and related families (e.g., Aristolochiaceae, Saururaceae, Lactoridaceae) have been shown to form the sister group to Winterales. The high species diversity within *Piper* is unique among the traditional Magnoliidae, providing a noteworthy example of an increase in diversification rate at the base of the angiosperms [9]. *Piper* species are distributed pantropically and take the form of shrubs, herbs, and lianas common in the understory of lowland wet forests. The greatest diversity of *Piper* species occurs in the American tropics (700 spp.), followed by Southern Asia (300 spp.), where the economically important species *Piper nigrum* L. (black pepper) and *P. betle* L. (betel leaf) originated. Patterns of distribution of *Piper* species vary from being locally endemic to widespread. There are several species restricted to a specific center of diversity (e.g., Andes, Central America) and others occur throughout the Neotropics or the Paleotropics. *Piper* is often a dominant element in the understory of tropical forests and found to be one of the five most speciose genera in select Neotropical forests [10,11]. Although the genus *Piper* is easy to recognize by a combination of vegetative and reproductive characters, the apparent uniformity of their diminutive flowers presents a significant challenge to developing an infrageneric classification. Inflorescence variation has been used to define taxa within *Piper,* especially in combination with other characters, such as in *Pothomorphe* where axillary umbellate inflorescences and flowers with two stamens serve to distinguish these species. The inflorescence in *Piper* is generally considered terminal, with the solitary type most common and also found among outgroup taxa. Theseplants belong to Kigdom: Planta, Division: Angiospermae, Class: Magnoliopsida, Order: Piperales, Family: Piperaceae, and Genus: Piper.

Members of Piper family are small trees, shrubs, or perennial or annual herbs. Plants are often rhizomatous, either terrestrial or epiphytic [12]. The stems can be simple or branched. Simple leaves have entire margins, are positioned at the base of the plant or along the stem, and the arrangement can be alternate, opposite. Stipulesare usually present, as are petioles. The leaves are often noticeably aromatic when crushed. Inflorescences (in the form of spikes) are terminal, opposite to the leaves, or located in the axils. Flowers are bisexual with no perianth, each flower is subtended by a peltate bract. Stamens are 2-6, and hypogynous, with 2-locular anthers. There are usually 3-4 stigmas attached to a single pistil per flower, which is 1 or 3-4 carpellate [13]. The ovary is one locular, and superior. Fruits are drupelike with a single seed per fruit. The seeds have a minute embryo, and mealy perisperm [14]. The genus Piper is the most representative of this family [15]. Black pepper is native to South East Asia of India, who is one of major producers. It can be also found cultivated inIndonesia, Malaysia and Brazil [16].

Piper has been used in various parts of world in an attempt to cure several diseases. In Table **1** we list the uses of the Piper in folk remedies, some include its use to combat infections, toothaches, diarrhea, burns, bronchitis and for wound dressing. A study on plants from Brazil also points out its properties to attack venereal diseases and bronchitis and its use as sedative and for wound healing [17]. In some African countries, the plant has been prescribed to treat dysentery, intestinalparasites, constipation and dyspepsia [18-21]. In Cameroon, it is a local remedy for digestive tract diseases [22]. In addition to its popular use for anti-diarrheic and anti-filiariasis. In Nigeria, a decoction of the plant is taken to treat diseases of poultry [23]. In Central Africa the plant is used to treat particularly intestinal parasites [24] while in Kava, it is used as relaxing drink [25]. In India, it is used in the treatment of asthma and chronic bronchitis [24]. In Argentina an infusion made of its fruit (*P. nigrum*) is used as anti-inflammatory [26] and in Colombia thisplant is particularly used for its antibiotic activity and to treat fever and diarrhea [27-29] Inpoultices against skin inflammations, burns, as an emetic, to reduce feveror whenbowel problems [30]. Inflorescence slices of *Piper Betle* L. are sandwiched between two halves of an areca nut (*Areca catechu*) as a betel quid and chewed by some people in south-east Oriental countries, including Taiwan, India, Thailand, Malaysia and the Philippines for cardiovascular disorders [31].

Known as the king of spices for many hundreds of years, pepper (*Piper nigrum*) is a trademark spice product of Kerala (India), which is exported to almost all parts of the world. Black pepper is one of the most versatile spices used in virtually in all savory cooking. In order to keep the fragrance and flavor intact, it is generally ground just before preparing dishes and added at the last minutes in the recipes. Consumption of dishes prepared with excessive amounts of

Table 1. Ethnomedical Uses of Different *Piper* Species Found World Wide.

Plant	Place Country	Part(s) Used	Ethno Medical Uses	Preparation(s)	Reference(s)
P. aduncum L		Leaves	Is used for inflammation, and as antiseptic	Decoction	[32]
P. alyreanum C.DC,	North and South America.		This plant has been used as an immunomodulator, analgesic and antide- present in folk medicine		[33]
P. amalago	Mexico	Fruit	Alleviate chest pain and inflammation	Infusion	[34]
P. amalago	Guatemala	Fruit	Gastrointestinal and chest pain	Infusion	[34]
P. anduncum	Brazil	Inflorescense	Is used against venereal diseases and urinary throat	Decoction	[35]
P. angustifolium	Perú	Leaves	Desinfection wounds and sores	Decoction	[36]
P. arboretum	Brazil	Inflorescense	Is used against general infections	Decoction	[35]
P. auritum	Mexico	Leaves	Chronic laryngitis, dyspnoea, counteract scorpion sting, asthma, diaphoretic, diuretic and stimulant, for tonsillitis, erysipelas, fevers, gout, antiblenorrágico, rheumatism and sores	Infusion	[37]
P. auritum	Cuba	Fruit	Antidiarrhea	Infusion	[38]
P.auritum	Colombia andCosta Rican	Leaves	Is used Pain, oral ulcers, anxiety and inflammations	Infusion	[16]
P. betle L.	Thailand, Taiwan, India, Malaysia, Philippines	Inflorescense Slices, leaves	As tonic. The leaves are also used as medicine for elephants	Chewed	[39]
P.betle	Taiwan	Fruits	Contraceptive	Powder mixed with borax	[40]
P. chaba H.	Thailand	Leaves	Antimalarial, anti-flatulent, expectorant	Infusion	[41]
P.chaba	India	Roots and fruits	Asthma, bronchitis, fever, abdominal pain, as dstimulant, and in hemorrhoidal afflictions	Infusion	[42]
*P. chaba*or *P. longum* Linn.	Thailand	Leaves	Carminative, element tonic, antidiarrheal	Decoction	[43]
P. capense Lf	*Comoro Islands*	Fruit	Diarrhea and cough	Infusion	[44]
P. dilatatum	Panama	Leaves	Tonic	Infusion	[35]
P. elongatum V	Peru	Leaves	Istread for symptoms of cutaneous leishmaniasis.	Decoction	[45]
P. guineense	Kenya	Fruit	Insecticidal, larvicidal and repellent	Infusion	[46]
P. guineense	West Africa	Fruit	Insecticidal	Infusion	[46]
P.guineense	South Africa	Fruits, leaves, roots, and seeds	Flavorant, treatment of bronchitis, gastrointestinal diseases, venereal diseases, and rheumatism	Preparation	[47]
*P.hispidum*Sw	Peru	Leaves	Is used as poultices for healing wounds and to tread the symptoms of cutaneous leishmaniasis.	Decoction	[45]

(Table 1) contd….

Plant	Place Country	Part(s) Used	Ethno Medical Uses	Preparation(s)	Reference(s)
P. jaborandi	Brazil	Leaves	Used as a local anaesthetic	Infusion	[17]
P. kadsura	Taiwan	Leaves	Treatment of asthma and arthritic conditions	Infusion	[31]
P. kadsura	China	Fruit	Asthma, arthritic conditions	Infusion	[48]
P. lanceaefolim	Colombia	Fruit	Skin infections	Infusion	[27]
P. longum	India	Roots	Treatment of asthma and chronic bronchitis	Infusion	[26]
P. longum	China	Leaves	Antihyperlipidemic	Infusion	[25]
P. longum	India	Fruits	Analgesisc, diuretic effects, relaxation of muscle tension and alleviation of anxiety	Infusion	[23]
P. longum	Asia, Pacific islands, India	Leaves, roots	Treatment of gonorrhea, menstrual pai, tuberculosis, sleeping problems, respiratory tract infections, chronic gut related pain and arthritic conditions	Infusion	[23]
P. longum L.	China	Leaves	Analgesic and treatment for stomach disease, antihyperlipidemic	Infusion	[49]
P. longum *P.nigrum*	Korean	Fruits	Have been used for the treatment of cholera, dyspepsia, various gastric ailments and arthritic disorders	Decoction or infusion	[50]
P. marginatum Jacq.	Brazil	Inflorescense	The same indication and used as above and against toothaches	Decoction	[35]
P. marginatum	Colombia, Costa Rica	Leaves	Inflammations, pain, oral ulcers, anxiety	Infusion	[46, 51]
P. methysticum	Europe, USA	Roots	Anxiolytic properties	Elixir, tinctures	[28]
P. methysticum	Kava, South Pacific	Roots	Used as relaxing drink prepared for ceremonial and recreational purposes	Elixir	[28]
P.methysticum	Taiwan, Fuchein	Fruits	Asthma, bronchitis, fever	Infusion	[42]
P.methysticum	Taiwan, Fuchein	Fruits	Asthma, bronchitis, fever	Infusion	[47]
P. nigrum	Brazil	Inflorescense	Is used against coughs and as tonic for appetite	Decoction or infusion	[16]
P. nigrum	Colombia	Fruit	Asthma, colon toxins, obesity, chronic indigestion, sinus congestion, fever, cold extremities, intermittent fever, cholera, colic pain, diarrhea, gastric ailments, worms and piles	Infusion	[43]
P. nigrum	Kurumilagy India	Fruits	Control dry cough	Powder fruit is taken with milk	[53]
P. nigrum	Argentina	Fruit	Anti-inflammatory	Infusion	[54]
P. nigrum	India	Fruit	Dyspnoea, cardiac diseases, piles, bronchitis and fever	Infusion	[54]
P. nigrum	West Africa	Fruit	Insecticidal	Infusion	[49]

(Table 1) contd….

Plant	Place Country	Part(s) Used	Ethno Medical Uses	Preparation(s)	Reference(s)
P.ovatum	Brazil	Leaves	It is used in traditional medicine for the treatment of inflammations and as an analgesic	Infusion	[55]
P. piscatorum	Brazil	Leaves, roots	As a fish poison, toothache remedy, and chewing tobacco substitute among numerous ethnic groups in Venezuela and Brazil	Infusion or chewed	[52]
P. piscatorum	Venezuela	Fruit	Toothache remedy and a fish poison	Infusion	[56]
P.pulchrum	Colombia	Fruit	Medicinal use in infections	Infusion	[57]
P.regnellii	Brazil	Leaves and roots	To treat wounds and reduce swelling and skin irritation	Infusion or plasters	[55]
P. ribesoides	Thailand northern and northeastern parts.	Stem	Used as carminative, antiflatulent, and tonic element.	Infusion	[40]
P.sylvaticum	India	Roots	Antidote to snake poison	Infusion	[40]
P. taiwanense	Taiwan	Leaves	Tonic	Chewing together with lime and catechu	[53]
P. tuberculatum	Brazil	Leaves	Sedative and as an antidote for snake-bite	Infusion	[52]
P. tuberculatum	West Africa	Fruit	Insecticidal	Infusion	[44]
P. tuberculatum	Brazil	Leaves	Sedative and antidote for snake-bite	Infusion	[52]
P. tricuspe	Colombia	Fruit	Antimalarial, snake-bite	Infusion	[56]
P. umbellatum	Santo Domingo	Leaves	External ulcers, abscesses	Decoction or infusion	[24]
P. umbellatum	Brazil	Inflorescense	Against kidney diseases	Decoction or infusion	[52]
P. umbellatum	Brazil, Ivory coast	Inflorescense	Women diseases, emmenagogue	Decoction	[52]
P. umbellatum	Brazil, Mexico	Root	Digestive tract, diarrhea, Poultice external	Maceration and drunk with white wine	[52]
P. umbellatum	CentralAfrica, Cameroon	Root	Digestive tract, dyspepsia, constipation, dysentery	Decoction	[20]
P. umbellatum	CentralAfrica, Cameroon, South-East Asia,Congo, Guinea, Jamaica, French Guyana	Leaves	Intestinal parasites	Decoction	[20]
P. umbellatum	Cameroon	Fruit	Treatment of poisoning, pitting oedema, foetal malpresentation, filiariasis, rheumartism, hemorrhoids and dysmenorrhea	Infusion	[58]
P. umbellatum	Brazil, Haiti, Republica Dominicana, Africa	Roots	Burns	Decoction	[22]
P. umbellatum	Brazil, Costa Rica, Malaysia	Leaves, roots	Bronchitis, cough	Tea, chewed	[21]
P. umbellatum	Brazil, Mexico, Cuba, Africa, Nigeria	Fruits	Filariasis, diarrhea, with blood stomachache, diseases of poultry	Decoction or infusion	[19]

black pepper can cause gastrointestinal irritation, and bleeding from the ulcer sites. Therefore, recipes prepared with pepper should be avoided in individuals with stomach ulcers, ulcerative colitis, and diverticulitis conditions. Peppercorns are rich source of electrolytes, vitamins, carotenes, minerals (Table **2**). Amongthe nutritional propertiesof black pepperalsobenoted thathas the followingnutrients: 10.90 g protein, 0.11mg vitamin B1, 0.24 mg vitaminB2, 1.10 mg Vitamin B3, 0.34mg vitamin B6 [59].

Table 2. *Piper nigrum* Nutritional Value/100g (USDA National Nutrient Data Base).

Principle	Nutrient	Value % of RDA
Energy	255 Kcal	13
Carbohydrates	64.81 g	49
Protein	10.95 g	11
Cholesterol	-	-
Dietary fiber	26.5	69
Choline	11.3 mg	2
Folic acid	10 µg	2.5
Niacin	1.142 mg	7
Riboflavin	0.109 mg	9
Thiamin	0.109 mg	9
Vitamin A	299 IU	9
Vitamin C	21 mg	35
Vitamin Eγ	4.56 mg	30
Vitamin K	163.7 µg	136
Sodium	44 mg	3
Potassium	1259 mg	27
Calcium	437 mg	44
Copper	1.127 mg	122
Magnesium	194 mg	48.5
Manganese	5.626 mg	244.5
Phosphorus	173 mg	25
Zinc	1.42 mg	13
β-Carotene	156 µg	-
β-Criptoxanthin	48 µg	-
Lutein-zeaxanthin	205 µg	-

3. PHYTOCHEMICAL OF *PIPER SPECIES*

Phytochemistry studies of *Piper* genus have demonstrated the presence of terpenes (mainly found in its essential oils), alkaloids, flavonoids and other classes of secondary metabolites. Since the isolation of piperine from *P. nigrum*, scientists have been searching for new physiologically active compounds in plants from the family Piperaceae and hundred of compounds belong to different classes have been isolated [60].

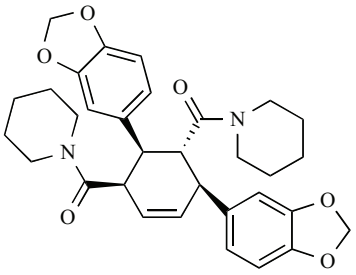
Pepper plants accumulate pungent bioactive alkaloids called piperamides. Piperamides are secondary metabolites present in the outer part of the fruits and in the seeds of black, white, green, and red peppers (*Piper nigrum* L.). The chemical structures of these compounds are shown in (Figs. **1**-**4**). Black pepper is produced from green unripe berries of the pepper plant; the fruits are dried after a heat treatment that releases browning enzymes from the cell walls; white pepper is obtained when fully ripe berries are dried with the outer pericarp removed; green peppers are harvested unripe and then air-dried or freeze-dried; and red peppers are harvested when mature. The piperanine content of the peppers fruit (*P. nigrum*) ranged from 0.3% for the ground white pepper to 1.4% in black peppercorns. The corresponding range for piperdardine was to 1.8% in black peppercorns; for piperlonguminine, to 1.0 in black peppercorns; and for piperyline, from 0.9% in ground black pepper. In contrast to large differences in absolute concentrations among the peppers, the ratios of piperines to total piperamide were quite narrow, ranging from 0.76% for black to 0.90% for white peppercorns, Thus, on average, the total piperamide content of the peppers consists of 84% piperines and 16% other piperamides [61]. Piperine alkaloids and piperlonguminine from *P. longum* L. showed effects in a Parkinson´s disease model, Liu *et al.*, [62] developed and validated a rapid, sensitive, and accurate UPLC-ESI-MS/MS method that involves protein precipitation for the simultaneous determination of piperine and piperlanguminine in rat plasma. The method was successfully applied in pharmacokinetic studies of piperine and piperlanguminine in rats after oral administration of alkaloids from *P. longum* L. with excellent sensitivity, good linearity of responses, and high precision and accuracy.

4. PHARMACOLOGY

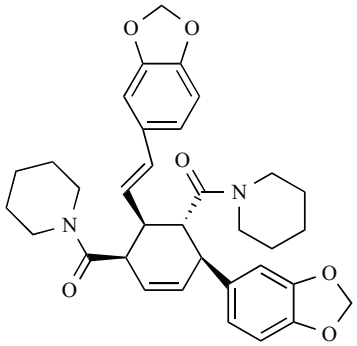
Piper have exhibited a wide spectrum of pharmacological activities. An overview of the modern pharmacological evaluations carried out on these species has been described in greater detail by a large number of researchers

4.1. Piperine

The fruits of *Piper nigrum* (black pepper) have been widely used since time immemorial in household spices and also in various traditional systems of medicine. According to the Ayurvedic system of medicine, *P. nigrum* fruits are used for anti-helmintic, anti-asthmatic, pain killer, insomnia relief, and epilepsy [66]. Studies have revealed its anticonvulsant [54] and bioavailability-enhancing propertiesofother drugs [73]. The fruits contain 5-9% alkaloids, the more important are: piperine, chavicine, piperidine, and piperetine [74]. Most of the pharmacological properties of black or white peppercorns of *P. nigrum* are attributed to a piperidine alkaloid, piperine, which is present in the fruits in amounts of 1.7-8% [75]. Little has been on the minor alkaloids, but the content of piperyline has been estimated as 0.2-0.3% and piperettine as



1
Nigramide A



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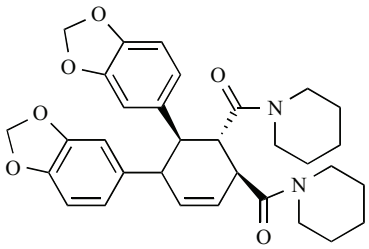

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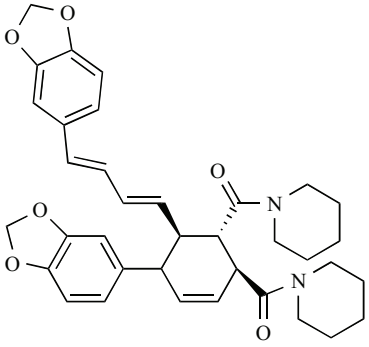

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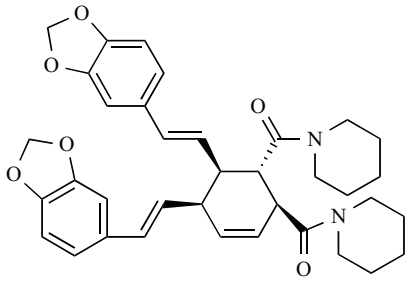

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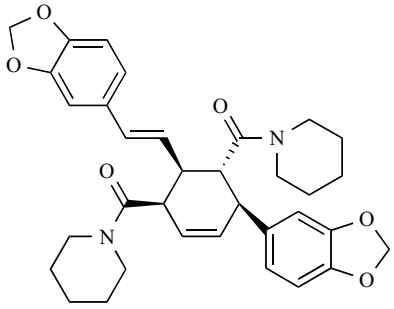

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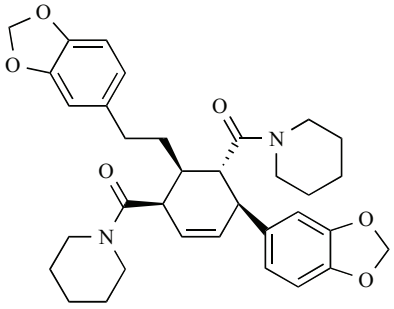

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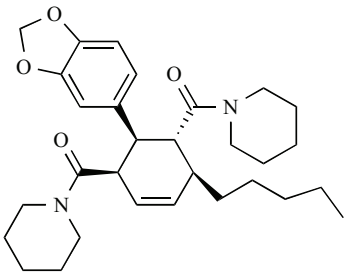

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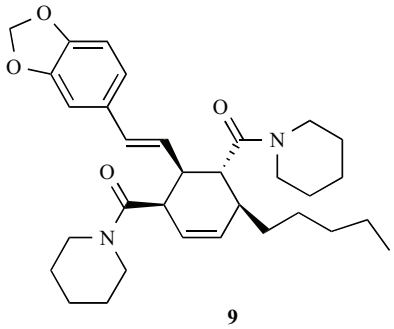

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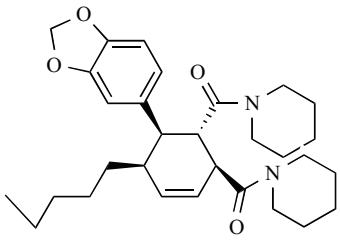

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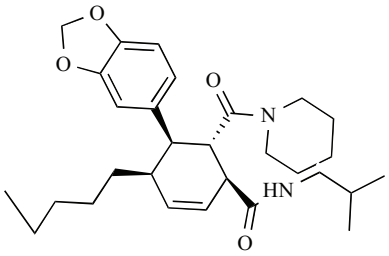

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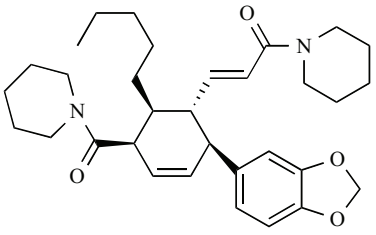

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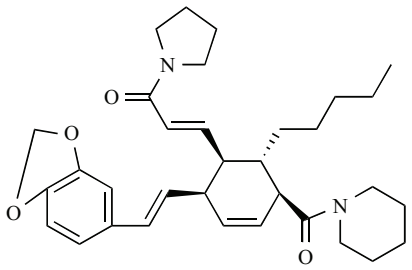
Nigramide L

Fig. (1). contd….



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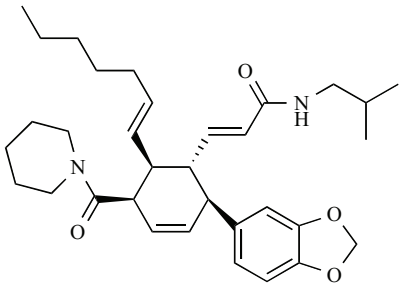

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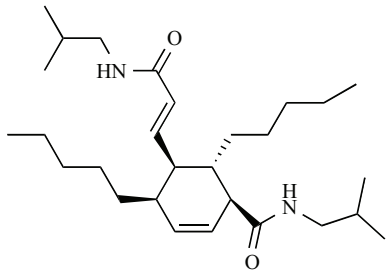

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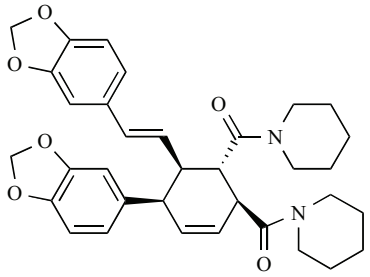

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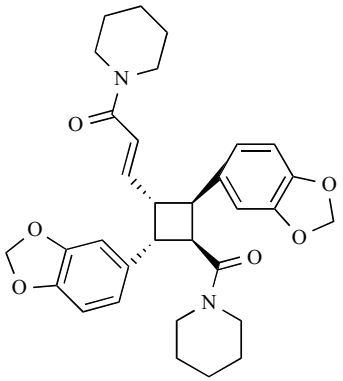
Nigramide P



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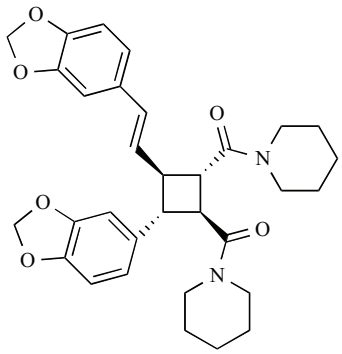

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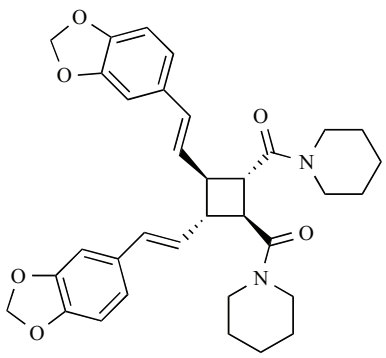
Nigramide R



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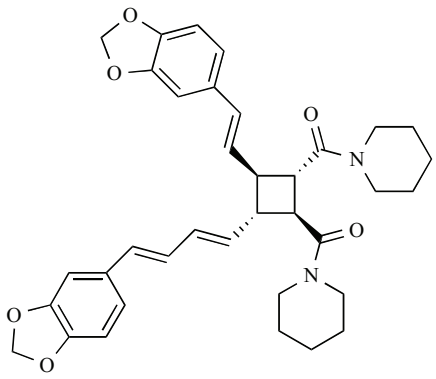
Nigramide S



20
Nigramide T

Fig. (1). Sixteen dimeric amide alkaloids possessing a cyclohexence ring, nigramides A-P, as four dimeric alkaloids possessing a cyclobutane, nigramides Q-T have been isolated from the root- *Piper nigrum* [63].

0.2-1.6% [76]. The quantity of piperine was elevated in fruits of *P. nigrum* and less in *P. betle*. A comparative piperine content in fruits from various Piper genusis presented in Table **3**.

Piperine, the main alkaloid in Piper genus, is responsible for much of the taste and smell of black pepper. It exhibits a wide variety of biological effects inc1uding anti-metastatic, antidepressant, hepatoprotective and antitumor. The anti-metastatic property of piperine in mice has been shown [80]. Additionally, the chemopreventive efficacy of piperine relating to a decrease in lipid peroxidation, protein carbonyls, nuc1eic acid and polyamine synthesis has also been reported. The bioavailability enhancing activity of piperine with various structurally and therapeutically diverse drugs has been studied by Khanjuria *et al.* [81]. The antioxidant efficacy of piperine was shown both *in vitro* [82], *in vivo*

[83], as well as its hepatoprotective ability [84]. Piperine was found to be cytotoxic towards Dalton's lymphoma ascites cells and Ehrlich ascites carcinoma cells [85].

Table 3. Comparative Piperine Content of Samples of Fruit from Various Piper

Type	Origin	Piperine Found (%)
Black pepper	Malasya (Sarawak) [77]	3.95
Black pepper	Indonesia (Lampong) [77]	5.84
Black pepper	India [77]	3.92
Black pepper	Sri Lanka [77]	6.38
White pepper	Indonesia (Muntok) [77]	5.48
Pepper oleoresins	Malasya [77]	40.8
Pepper oleoresins	Indonesia (Lampong) [78]	35.7
Pepper oleoresins	India [79]	42.9
Black pepper	India (Maharashtra) [79]	4.5
White pepper	India (Maharashtra)	3.3
P. longum	India (Maharashtra) [79]	3.7
P. retrofractum	India (Maharashtra) [79]	2.3
P. cubeba	India (Satara) [79]	1.2
P. betle	India (Maharashtra) [79]	0.9
P. colubrinum	India (Sreekara) [79]	4.9

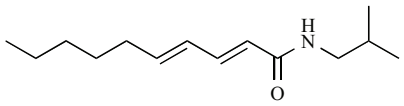
Piperine, was evaluated for its thyroid hormone and glucose regulatory efficacy. Adult male Swiss albino mice were daily administered Piperine at a dose of 2.50 mg/kg for 15 days, after that time serum levels of both the thyroid hormones, thyroxin (T4) and triiodothyronine (T3) as well as glucose concentrations were lowered [83]. Other study showed that its ingestion canmodulate the levels of apolipoprotein and insulin resistance in rat [86, 87].

In addition, Piperine demonstrated significant immunostimulation exhibited both anti-oxidative and anti-apoptotic potential. The effect of Piperine on the absorptive function of the intestine was studied by Johri *et al.*, [86]. Piperine could alter the structural relationship between lipids and protein (fluidity) interacting with the lipid environment to produce effects which lead to increase permeability of the intestinal epithelial cells. It was reported to inhibit the activities of rat hepatic monooxygenases and UDP-glucuronyltransferase. The study explores further the basis ofinhibition of glucuronidation. Piperine caused a concentration-related decrease in UDP-glucuronic acid content and the rate of glucuronidationin the cells. It was required less Piperinethan D-galactosamine to diminish the endogeneous level of UDP-glucuronic acid. The rate of glucuronidation of 3-hydroxybenzo (a) pyrene was dependent on the endogeneous level of UDP-glucuronic acid. At 50 μM of piperine, the rate of glucuronidation was reduced to about 50% of the basal rate. Piperine induced a noncompetitive inhibition of hepatic microsomal UDP-glucuronyltransferase with a Ki value of 70 μM. The studies demonstrate that Piperine modifies the rate of glucuronidation by lowering the endogeneous UDP-glucuronic acid content and also by inhibiting the transferase activity [87]. Piperine has previously been shown to inhibit several cytochrome P450-mediated pathways and phase II reactions in animal models [88]. Accordingly, treatment of rodents with Piperine resulted in increased plasma concentrations of several compounds such as theophylline, phenytoin, rifampin, and propanolol [73, 89]. Very recently, it was shown that asingle administration of 1 g of blackpepper more than doubledarea underthe plasma concentration-time curve and elimination half-life of phenytoin [90].

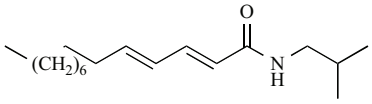
Treatment withpiperine using streptozotocin-induced diabetic Sprague-Dawley rats as a model of oxidative damage reversed the diabetic effects on GSSG concentration in brain, on renal glutathione peroxidase and superoxide dismutase activities, and on cardiacglutathionereductase activity and lipid peroxidation. Piperine treatment did not reverse the effects of diabetes on hepatic GSH concentrations, lipid peroxidation, or glutathione peroxidase or catalase activities; on renal superoxide dismutase activity; or on cardiac glutathione peroxidase or catalase activities. These data indicate that sub-acute treatment with Piperine for 14 days is only partially effective as an antioxidant therapy in diabetes [91]. Interest in piperamides arises from the fact that they were reported to inhibit enzymes that catalyze the biotransformation of nutrients and drugs, thus enhancing their bioavailability and effectiveness [92].

Piperine, is a known inhibitor of various enzymes (CYP isozymes) responsible for biotransformation of drugs. By inhibiting the metabolism of drugs, Piperine improves the bioavailability of drugs. Piperine significantly increased the dose-dependent antinociceptive activity of ibuprofen evaluated by both acetic acid writhing and formalin test, when it was administered with ibuprofen. Ibuprofen plasma concentration was also increased when it was administered with piperine. The synergistic antinociception activity of ibuprofen when administered with Piperine can be attributed to increased plasma concentration of ibuprofen. So piperine can be used as a bioenhancer along with ibuprofen [93].

Over-expression of P-gp, MRP1 and BCRP in tumor cells is one of the important mechanisms leading to multidrug resistance (MDR), which impairs the efficacy of chemotherapy. P-gp, MRP1 and BCRP are ABC (ATP-Binding Cassette) transporters, which can expel a variety of lipophilic anti-cancer drugs and protect tumor cells. Piperidine and piperine can potentiate the cytotoxicity of anti-cancer drugs in resistant sub-lines, such as MCF-7/DOX and A-549/DDP, which were derived from MCF-7 and A-549 cell lines. At a concentration of 50 μM Piperine could reverse the resistance to doxorubicin 32.16 and 14.14 folds, respectively. It also re-sensitized cells to mitoxantrone 6.98 folds. In addition, long-term treatment of cells by Piperine inhibits transcription of the corresponding ABC transporter genes. These results suggest that Piperine can reverse MDR by multiple mechanisms and it may be a promising lead compound for future studies [94].



21
Pellitorine



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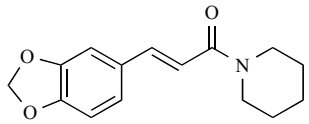
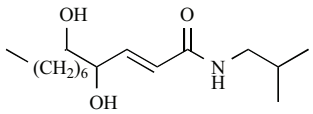
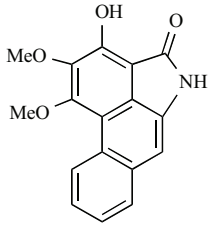
2,4-Tetradecadienoic acid isobutyl amide



23
(E)-1-[3′-4′-(methylenedioxy)-cinnamoyl]piperidine



24
Sylamide



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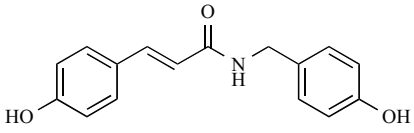
Piperolactam D



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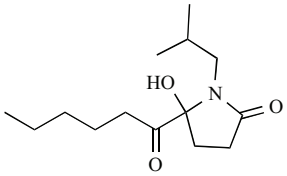
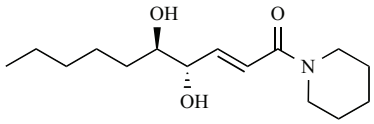
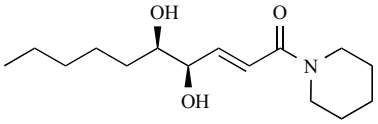
Paprazine



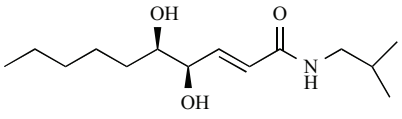
27
N-isobutyl-4-hexanoyl-4-hydroxypyrrolidin-1-one



28
(±)-*erythro*-1- (1-oxo-4,5-dihydroxy-2E decaenyl)piperidine



29
(±)-*Threo*-1-(1-oxo-4,5-dihydroxy-2E-decaenyl)piperidine



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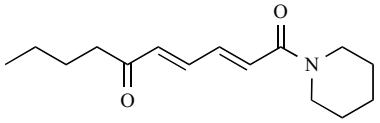
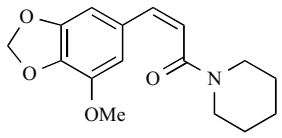
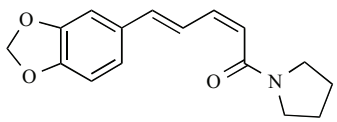
(±)-*Threo*-N-isobutyl-4,5-dihydroxy-2E-octaenamide



31
1-(1,6-dioxo-2E ,4E-decadienyl)piperidine

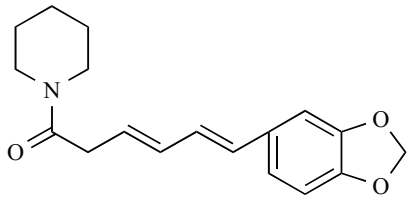


32
1- [l-oxo-3(3,4-methylenedioxy-5-methoxyphenyl)-2Z-propenyl]piperidine

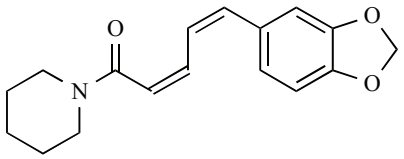


33
1-[1-oxo-5(3,4-methyl-enedioxyphenyl)-2Z,4E-pentadienyl]pyrrolidine

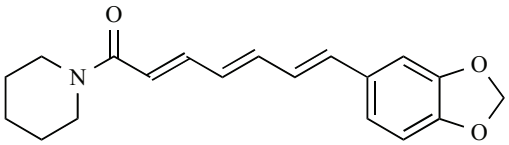
Fig. (2). Alkaloids from roots of *Piper nigrum* [64-66].



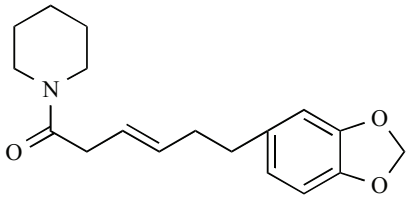
34
Piperine



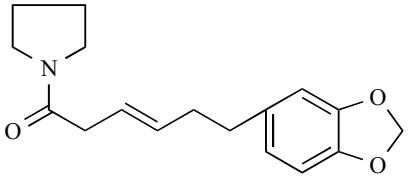
35
Chavicine



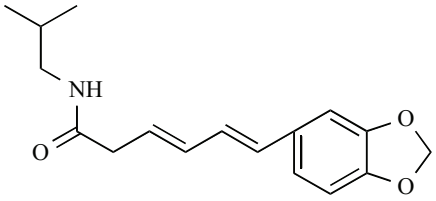
36
Piperettine



37
Piperanine



38
Piperyline



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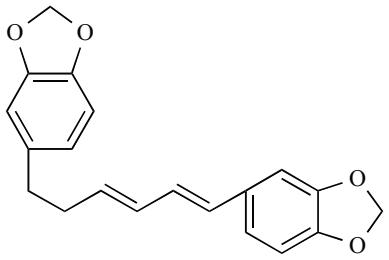
Pipelonguminine



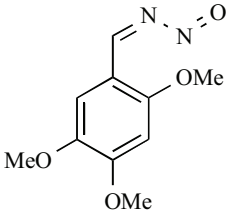
40
Piperdardine

Fig. (3). Piperamides from *P. nigrum* fruit [61, 67].

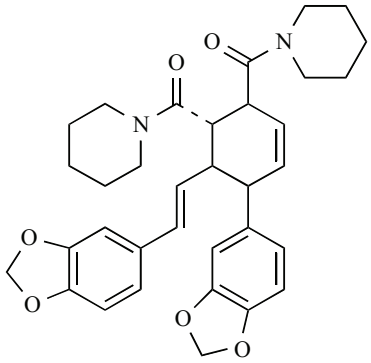
4.2. Anticancer/Antitumor

In recent years, considerable emphasis has been focused on identifying new cancer chemopreventive agents, which could be useful in humans. Furthermore, Piperine was evaluated for its chemopreventive effect, was found to suppress benzo(a)pyrene (B(a)p) induced lung cancer in Swiss albino mice. In lung cancer bearing mice, altered levels of total protein and protein bound carbohydrate components (hexose, hexosamine and sialic acid) were observed in serum, lung and liver tissues. Dietary supplementation of piperineto animals decreased the total protein and protein bound carbohydrate levels of lung cancer bearing animals in during initiation and post-initiation phases. These data suggest that Piperine may extend its chemopreventiveeffect through modulating the protein bound carbohydrate levels, as they are one of the indicators of tumorigenesis [95].

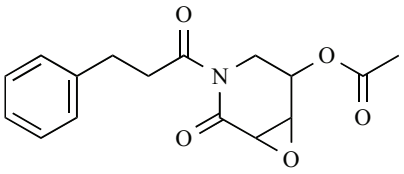
Piperine supplementation exhibit significant effects against B(a)p induced lung carcinogenesis. Piperine significantly reduced the levels of hydrogen peroxides in cancer animals. Supplementation with Piperine enhances antioxidant status and other seleno-proteins [96]. Antioxidant



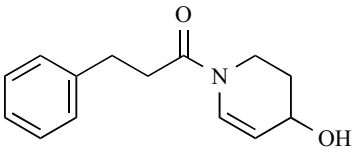
41
1-Nitrosoimino-2,4,5-trimethoxybenzene
Roots of *P.sarmentosum*



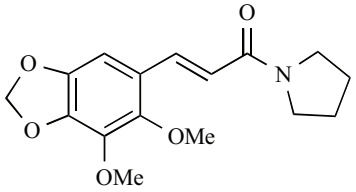
42
Chabamine
Stems of *P. chaba*



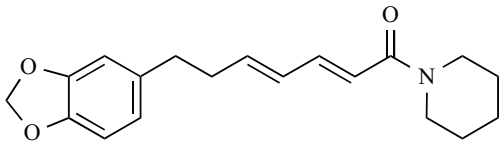
43
3a,4a-epoxy-5b-pipermethystine
Leaves of *P.methysticum*



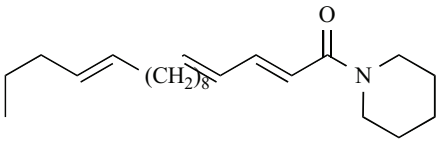
44
Awaine
Leaves of *P. methysticum*



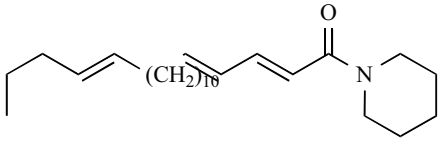
45
Peepuloidin
Leaves of *P. peepuloide*s



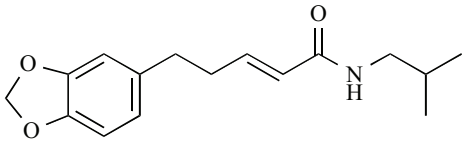
46
Piperdardine
Leaves of *P. Tuberculatum*



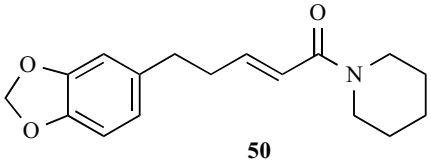
47
2E,4E,14Z)-N-(2,4,14-octadecatrienoyl)piperidine
Fruits of *P.retrofractum*



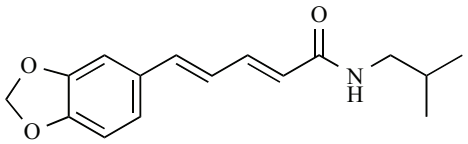
48
(2E,4E,16Z)-N-(2,4,16-eicosatrienoyl)piperidine
Fruits of *P. retrofractum*



49
Dihydroperlongumine
Kernels of *P. negrum*



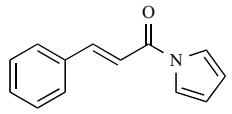
50
Dihydropiperine
Kernels of *Piper negrum*



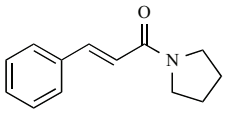
51
Dihydroperlongumine
Kernels of *P. negrum*

Fig. (4). Alkaloids from other Piper [65, 68, 69].

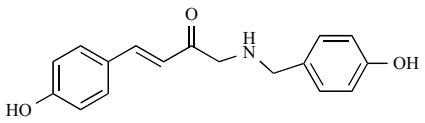
(Fig. 4) contd….



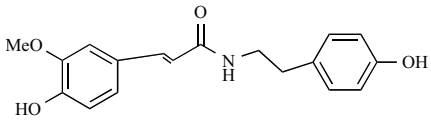
52
N-Cinnamoylpyrrole
P.argyrophyllum



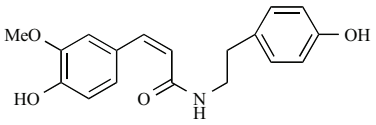
53
N-Cinnamoylpyrrolidine
P.argyrophyllum
P. schmidtii



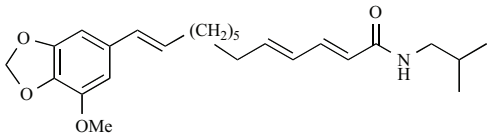
54
N-p-Coumaroyltyramine
P.argyrophyllum



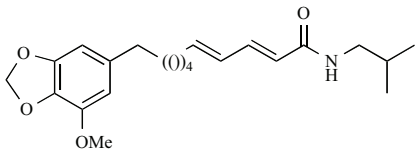
55
N-cis-Feruloyltyramine
P.argyrophyllum



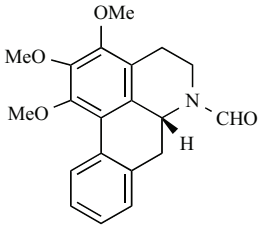
56
N-trans-Feruloyltyramine
P.argyrophyllum



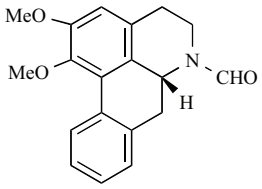
57
Guineensine
P.longum



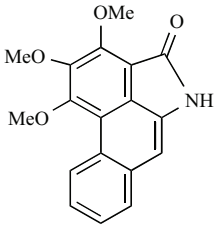
58
(2E, 4E)-N-Isobutyldecadienamide
P. pedicellosum



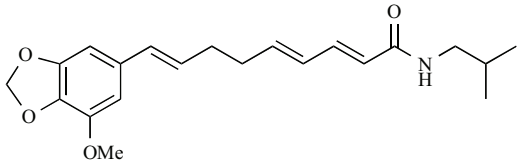
59
z)-(E)-N-Formylmouragines
P.argyrophyllum



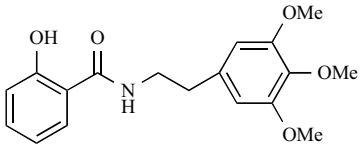
60
(z)-(E)-Formylnornuciferines
P.argyrophyllum



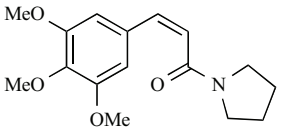
61
Cepharanone B
P. acutisleginum



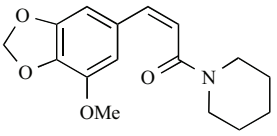
62
Retfractamide A
hydroxybenzamide
P. hispidum



63
N-2-(3'4',5'-trimethoxyphenyl)ethyl-2-
P. manii, P. longum



64
Sarmentomicine
P. sarmentosum



65
g-Asarone
P. sarmentosum

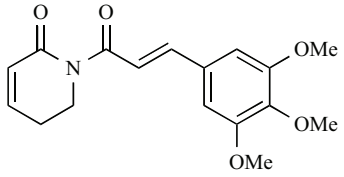
Fig. (4). Alkaloids from other Piper [65, 68-71].

enzymes reduce the carcinogen DNA interaction by providing large nucleophilic pool for the electrophilic carcinogens. Since B(a)p is also one of the electrophilic carcinogens [97], the above evidence may hold good for Piperine which exerts its anticancer effects through its antioxidant properties. The levels of DNA-single strand breaks and DNA-protein cross links were found to be high in B(a)p induced lung cancer bearing animals when compared to control animals. The formation of DNA-protein cross links induced by B(a)p can be attributed to the free radicals produced during the metabolism of B(a)p who can oxidize protein amino acid residues that leads to DNA cross-linking. Therefore oral supplementation with Piperine can modulate phase-II enzyme activities and reduce DNA damage and DNA-protein cross linking in B(a)p induced lung carcinogenesis in a swiss albino mice model [98]. This unique association between oxidative stress induced in cancer bearing host and Piperine supplementation may help us to understand the chemo-preventive ability of Piperine against cancer. Additionally, Piperine inhibits lung metastasis induced by B16F-10 melanoma cells, with a 95.2% inhibition of tumor nodules compared to the untreated mice control group. Tumor nodules are metastatic colonies of Bl6F-10 melanoma cells formed in the lungs and initiate lung fibrosis and collagen deposition. This inhibition of tumor nodules correlated with an increase in the life span of the metastatic-tumor-bearing animals and this can be due to the inhibition of oxygenase and/or p-450 isoenzymes [99].

To evaluate the effect of Piperine on the production of nitric oxide (NO) and tumor necrosis factor-α (TNF-α) level was analyzed using Balb/C mice. The level of nitrite in the lipopolysaccharide (LPS) stimulated Balb/C mice was reduced in the Piperine treated animals, who also showed a drastic reduction of TNF-α. The same result was obtained with Con-A induced TNF-α production. Piperine could inhibit the nitrite production by *in vitro* activated macrophages at concentration of 5 µg/ml. *In vitro* L929 bioassay also revealed the inhibition of TNF-α production by the Piperine treatment [100].

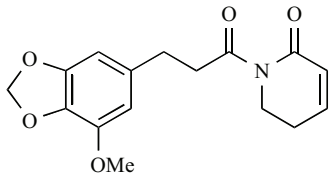
In another report, Piperine was toxic to Dalton's lymphoma ascites (DLA) to Ehrlich as cites carcinoma (EAC) cells. Piperine was found to be cytotoxic towards DLA and EAC cells. Alcoholic extract from *P. nigrum* fruit and piperine was also found to produce cytotoxicity towards L929 cells. Piperine was found to increase the circulating antibody titer and antibody forming cells indicating its stimulatory effect on the humoral arm of immune system. Immunornodulators may activate cytotoxic effector cells, such as cytotoxic T lymphocytes, natural killer (NK) lymphocytes, macrophages, and activated neutrophils. Use of chemotherapy plus target-specific immunomodulators hold a reasonable promise for clinical utility in future. Immunomodulatory activity of Piperine may be due to the combined action of humoral andcell-mediated irnmune responses. Hence, the results indicated that it could act as a non-toxic immunomodulator with antitumor properties [101]. Bezerra *et al.*, [102] reports the antitumor activity of Piplartine and Piperine on mice transplanted with Sarcoma 180. Piplartine has shown antiproliferativeeffects *in vitro,* and is more potent than Piperine [103]. Sarcoma 180 is a mouse-originated tumor and one of the most frequently used cell lines in antitumor-related research *in vivo* [104]. Their antitumor activity involves the activation of cellular and humoral immune responses and probably also due to NF-KB inhibition and pro-inflammatory cytokine gene expression induction [105]. Piperine is only mildly cytotoxic, indicating that its antitumor activity is not related to direct anti-proliferative effect on tumor cells. The mechanisms involved has not been elucidated yet. Moreover, Dogra *et al.* [80], demonstrated that Piperine at 4.5 mg/kg has a consistent immunosuppressive effect, suppressing the weight and cell population of the spleen of treated animals.

Piplartine seems to be different from Piperine, immunohistochemical results obtained with Ki67 staining showed that its antitumor activity is associated with a reduction inthe tumor proliferation rate, which is compatible with its antiproliferative effects. Piplartine had no effect on the spleen of treated animals, and apparently its main toxicological target is the kidney. Both Piplartine and Piperine possess *in vivo* antitumor activity related to reversible toxic effects on liver and kidney [106]

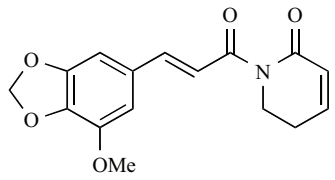


66
Piplartine

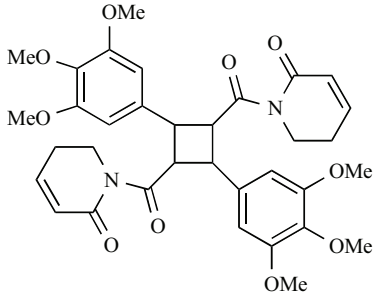
Piplartine and Piperine were administered in combination with the chemotherapeutic agent 5-fluorouracil (5-FU) to test their antitumor activity using different cells: HL-60, MDA-MB435, SF295 and HCT-8 were tested with 5-FU in the absence and presence of Piplartine or Piperine. The results showed in both combinations, a bigger tumor growth inhibition. Piplartine produced stronger effects in all cell lines tested. Piperine, in contrast, only increased 5-FU cytotoxicity in HL-60 and MDA-MB435 cell [80]. Bioactive-guided fractionation of chloroform extract of the leaves of *Piper aborescens* afforded a five cytotoxic pyridine alkaloid N-(3-methoxy-4, 5-methylenedioxycinnamoyl)- Δ^3 -pyridin-2-one, piplartine and piplartine dimer A which showed significant cytotoxicity against the growth of A-549, HT-29, KB and P-388 cells. Instead, N-(3,4-dimethoxycinnamoyl-Δ^3 -pyridin-2-one and N-(3-methoxy-4,5-methylenedioxydihydro-cinnamoyl)-Δ^3-pyridin-2-one, only exhibited cytotoxicity against P-388 andHT-29 [107].



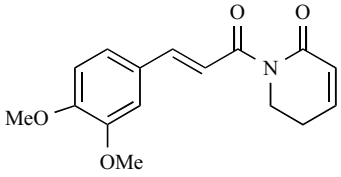
67
N-(3-methoxy-4,5-methylenedioxydihydrocinnamoyl)-D^3 -pyridin-2-one



68
N-(3-methoxy-4, 5-methylenedioxycinnamoyl)-D^3 -pyridin-2-one

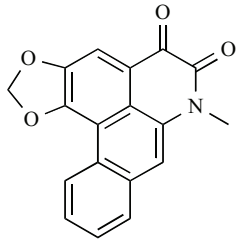


69
Piplartine dimer A



70
N-(3,4-dimethoxycinnamoyl)-D^3 -pyridin-2-one

A bioassay-guided using a methanol extract of *Piper caninum* resulted in the isolation of alkaloid cepharadione A. The activity of cepharadione A in the RAD52 yeast assay implies that it can induce double-strand DNA damage in an intact eukaryotic cell. Thus, the cytotoxicity noted for cepharadione A may derive from its DNA-damaging activity. Using a similar, but less sensitive agar diffusion yeast assay, has identified several other oxoaporphine alkaloids as putative double-strand DNA-damaging agents and DNA topoisomerase inhibitors [33].



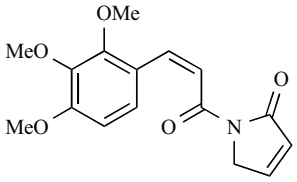
71
Cepharadione A

Furthermore, was reported the cytoprotective effect of piperine against cisplatin-induced apoptosis in HEI-OCI cells. Piperine-induced HO-I expression was directly related with JNK pathway because the inhibitor, SP600125, blocked the expression completely. ARE-mediated phase II drug metabolism gene expressions was done via the JNKl- and Nrf2-dependent pathways. Therefore, these results demonstrate that the induction of HO-I expression by piperine may serve as one of the important mechanisms for the protective effect of piperine on cisplatin-induced apoptosis. In conc1usion, the piperine induces HO-l expression via Nrf2 and JNK pathway, and HO-l express ion by piperine could contribute to cellular defense mechanism against cisplatin-induced apoptosis. Inthis respect, the search for potent inducers of HO-l from nontoxic food materials may be attributed to decrease the ototoxic side effect of cisplatin [108].

Piperine at a concentration of 50 μg/mL was found to produce cytotoxicity in cultured L929 mouse fibroblast cells, and it could inhibit the development of solid tumors in mice when they are induced with Dalton's lymphoma ascites cells. Ascites tumor-bearing animals survived only 15 days after the tumor induction while the Piperine-treated animals survived 23.8 days with an increase in life span of 58.8%. Certain studies have shown that Piperine could also inhibit the metastasis induced by B16F10 melanoma cells [109]. Piperine inhibits PBMC proliferation at an $IC_{50}$of 100.73 μg/ml, compared to its activity in various human leukemic cell lines (IC_{50}ranging from 17 to 57 μg/ml). Piperine has been shown to inhibit eosinophil infiltration and airway hyperresponsiveness by suppressing T cell activity and Th2 cytokine production in an ovalbumin-induced asthma model [110]. However, it also caused an increase in the circulating antibody titer and antibody-forming cells, as well as enhanced bone marrow cellularity and α-esterase.

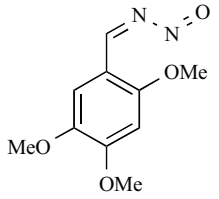
Prostate cancer harbors profound sensitivity to the body's androgen milieu and it is considered the most endocrine-dependent solid neoplasm [111]. Since androgens are essential oncogenic promoters in prostatic carcinoma, modulation of androgen signaling pathways represents a rational approach to prostate cancer therapy. Although ADT remains the mainstay therapy for patients with both localized and advanced disease, in most patients PC eventually progresses to a castration-resistant form (CRPC) [112]. Aberrant signaling of androgen-dependent pathways likely plays a major role in the mechanism of ADT resistance. Piperlongumine (PL), a natural alkaloid abundantly present in the fruit of the Long pepper (*Piper longum*), which has insecticidal and antibacterial properties in addition to its ability to inhibit ethanol-induced gastric lesions in experimental animal models [113,114]. Recent studies demonstrate that PL can also inhibit growth of tumor cells of various origins both *in vitro* and *in vivo* [115]. Importantly, administration of PL does not cause any obvious adverse effects [116]. PL induces rapid AR depletion in prostate cancer cells through a proteasome-mediated reactive oxygen species (ROS)-dependent pathway, which coincides with reduced functional activity of AR signaling. Thus, PL has the potential to inhibit prostate carcinogenesis at both initiation and advanced disease stages via depletion of the AR alone or in combination with ADT regimens, affording novel therapeutic opportunities. Langkamide, and piplartine were isolated from the roots and stems of the shrub *Piper sarmentosum* Roxb. Which showed ability to inhibit HIF-2.

Bothcompounds inhibited HIF-2 transcriptional activity with EC_{50} values of 14.0, and 60.6 μM, respectively, for langkamide, andpiplartine. Piplartine showed moderate cytotoxicity with IC_{50}values of 61.4 μM, while langkamide showed no cytotoxicity at the highest dose tested (66 μM). Other agents, that have been shown to inhibit HIF-2α, include ibuprofen which inhibited endogenous HIF-2α in a dose dependent manner in the renal 786-o cell line and Neovastat (*Æ*-941) which inhibited HIF-2α expression in lung tissue in asthmatic BALB/c mice [117].

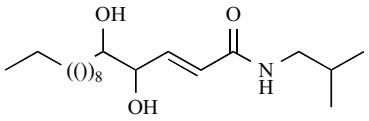


72
Langkamide

The roots of *Piper sarmentosum* have resulted in an aromatic compound, 1-nitrosoimino-2,4,5-trimethoxybenzene. *Piper nigrum* roots gave pellitorine, (E)-1-[3',4'-(methylenedioxy) cinnamoyl]piperidine, 2,4-tetradecadienoic acid isobutyl amide, piperine, sylvamide, cepharadione A, piperolactam D and paprazine. Pellitorine, was found to be extremely cytotoxic towards the MCF-7 cell line with an IC_{50} value of 1.8 mg/ml, but slightly less toxic against the HeLa cell line with an IC_{50} value of 13 mg/ml. 1-nitrosoimino-2,4,5-trimethoxybenzene gave an equally good activity for HeLa and MCF-7, and there could be due to contribution a the imino group [118].



73
1-nitrosoimino-2,4,5-trimethoxybenzene



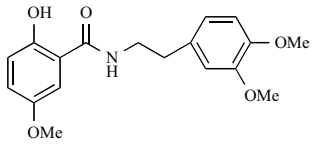
74
Sylvamide

The cytotoxicity assay of silver nanoparticle loaded with P. *longum*was measured using HEp-2 cell line by MTT test. *P. longum* extract is capable of producing silver nanoparticles in room temperature. Significant cytotoxic effect with a valueof 94.02% was observed at 500 μg/ml concentration of silver nanoparticles, whereas, at 31.25 μg/ml 51% death (49% viability) was observed. Earlier studies conformed that *in vitro* antiproliferative property of piperidine from *Piper nigram* against HEp2 cancer cell line [119]. It was also reported that the extract of *P. nigrum* and *Piper betle* have cytotoxicity activity against HL60 and HeLa cell line. Since lower doses of silver nanoparticles reduced by plant extracts are efficient in exerting cytotoxic effect on HEp-2 cell line silver nanoparticlesmay potentially prove to be useful as nanomedicine for anti-cancerous drug preparations [120].

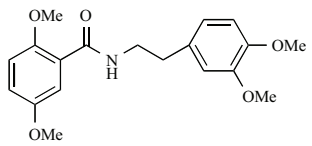
4.3. Anti-Platelet Aggregation

The chloroform extract of *P. Taiwanense*showed the most potent inhibitory effect on platelet aggregation *in vítro* than any other Piperspecies in Taiwan. Subsequent investigation of the chloroform extractled to the isolation of the alkaloid piperolactam A-C, 1-cinnamoyl pyrrolidine and 1-(*m*-methoxycinnamoyl) pyrrolide. All compounds at 100μM showed complete or nearly complete inhibition of platelet aggregation induced by arachidonic acid. Piperolactam B and 1-cinnamoyl pyrrolidine were more potent, and even at 50 μM showed complete inhibition of platelet aggregation, with IC_{50} value 30.9 and 30.5μM respectively [50,121].

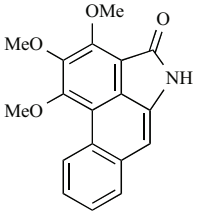
In another report, the methanolic extract of *Piper lolot*was subjected to activity-guided isolation to yield piperlotine A-L, that showed a potent antiplatelet aggregation activity after induction by arachidonic acid [122]. At 100 μg/ml compounds A,C,D, E showed 100% inhibitionof platelet aggregation by arachidonic acid with IC_{50} of 7.3 μg/ml comparable with aspirin (IC_{50} value 5.5 μg/ml). The amides containing a pyrrole or pyrrolidine ring are more active than other compounds, suggesting that the five member ring is important for the antiplatelet aggregation activity.



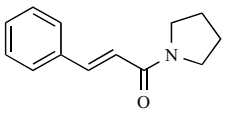
75
Piperolactam A



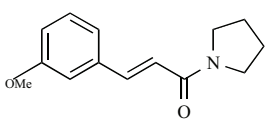
76
Piperolactam B



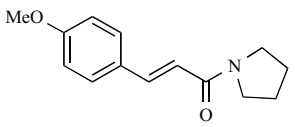
77
Piperolactam C



78
1-Cinnamoyl pyrrolidine



79
1-(m-methoxycinnamoyl) pyrrolide



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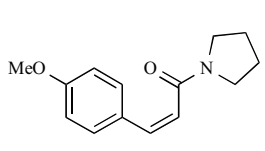
Piperlotine A



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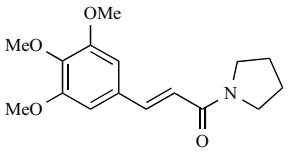
Piperlotine B



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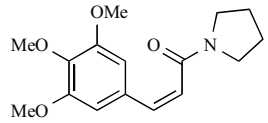
Piperlotine C



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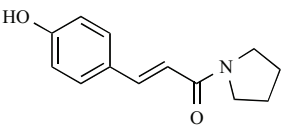
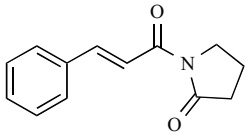
Piperlotine D



84
Piperlotine E



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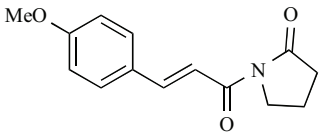
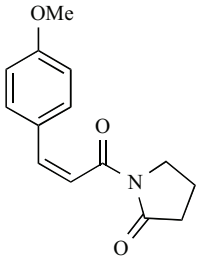
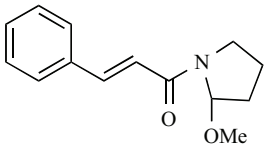
Piperlotine F



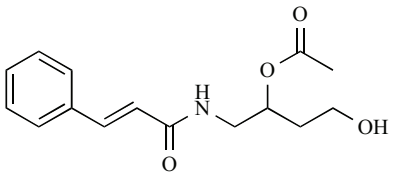
86
Piperlotine G



87
Piperlotine H



88
Piperlotine I



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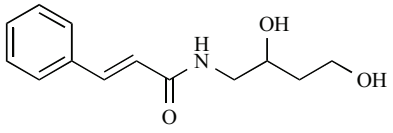
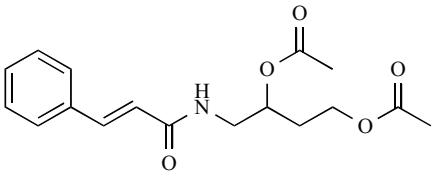
Piperlotine J



90
Piperlotine K

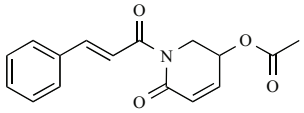


91
Piperlotine L

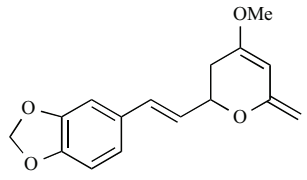
4.4. Hepatotoxicity

Piper methysticum Forst, is a p1ant indigenous to many islands of the South Pacifico The roots of this p1ant have been used in the form of a beverage, known as Kava, Kawa, or Awa, by natives of many of these is1ands to allay anxiety and reduce fatigue. Other uses chaimed for Kava bave been as an aphrodisiac, antiseptic, tonic, anodyne, sudorific, diuretic, stimu1ant, and intoxicant. Local application of the drug is reported to produce a burning pain followed by loss of sensitivity. Perhaps the most significant biological effects produced by extracts of this p1ant are the induction of intoxication of a si1ent and drowsy nature, accompanied by incoherent dreams when 1arge doses are ingested [123]. Kava (*Piper methysticum*) herbal supplements have been recently associated with acute hepatotoxicity. It is suspected that somekavalactones and no kavalactoneconstituents, such aspipermethystine, and flavokavain B identified from kavaare responsible for thehepatotoxicityso ina study byTeschkeetal., [teschke] found that The most important issues are certainly quality aspects ofthe kava raw material, especially regarding adulterantsand impurities of some kava products. To date, there have been no thorough evaluations of plant or productcontamination by ochratoxin A or *Aspergillus* varieties, which produce atlatoxins being toxic and carcinogenicto the human liver. Hepatitis due toatlatoxicosis inconnection with food contamination in various countriesis a well-establishedhuman liver disease, raising the question as to whether a similar mechanism or the presence of other mould hepatotoxins may be responsible for human kava hepatotoxicity [124].

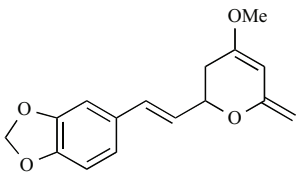
Nerukar *et al.*, [125] studiedthe effects of a major kava alkaloid, pipermethystine, present mostly in the leaves and stem peelings. Exposure of pipermethystine to human hepatomacells, HepG2, caused cell death and significantly decreased cellular ATP levels, mitochondrial membrane potential, and induced apoptosis as measured by the release of caspase-3 after 24 h of treatment. These observations suggest that pipermethystine, rather than kavalactones, is capable of causing cell death, probably in part by disrupting rnitochondrial function. Thus, pipermethystine may contribute to hepatotoxic reactions to kava.



92
Pipermethystine



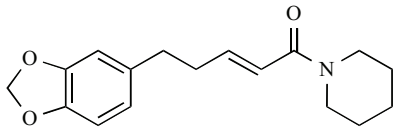
93
Dihydromethysticin



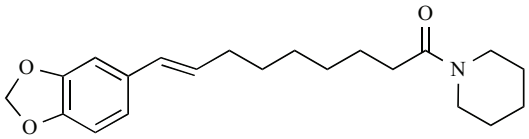
94
Desmethoxy-yangonin

4.5. Hepatoprotective

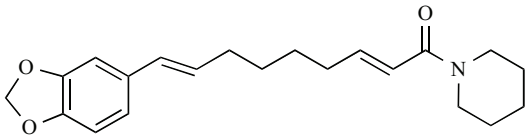
From a methanolic extract from the fruit of *Piper chava*it were isolated some amides: piperchabamides A-D, piperoleine B, piperanine, piperine, pipernonaline, piperlonguminine, retrofractamides A-C, guineensine, piperchabamides B, E, D, N-isobutyl-(2E,4E)-deca-dienamide, N-isobutyl-(2E,4E)-dodecadienamide and N-isobutyl-(2E,4E, 14Z)-eicosatrienamide. Most of them significantly inhibit cell death induced by D-GaIN/TNF-α in the hepatocytes at concentrations in the range of 1-30 μM. Notably, compounds piperchabamide B, piperlonguminine, retrofractamide C, piperchabamide D, and retrofractamide Bshowed strong effects at 3 μM with more than 50% inhibition. However, several amide constituents such as retrofractamide C, piperchabamide D, and retrofractamide B, exhibited no concentration-dependent inhibition at 4-30 μM, suggesting that these showed cytotoxic effectsat higher concentrations. Regarding "structure-activity" relationships, the amide moiety and the 1,9-decadiene structure between the benzene ring and amide moiety were suggested to be important for the strong inhibition of D-GalN/tumor necrosis factor-α (TNF-α)-induced death of hepatocytes. Furthermore, piperine, dose-dependently inhibited increase in serum GPT and GOT levels at doses of 2.5-10 mg/kg in D-GaIN/LPS-treated mice, and this inhibitory effect was suggested to depend on the reduced sensitivity ofhepatocytes to TNF-α [126].



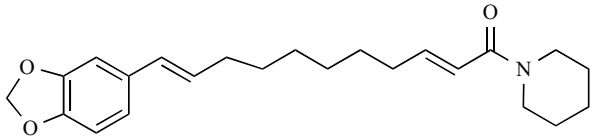
95
Piperanine



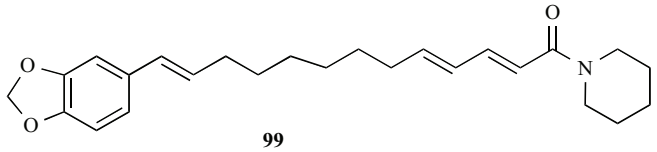
96
Piperoleine B



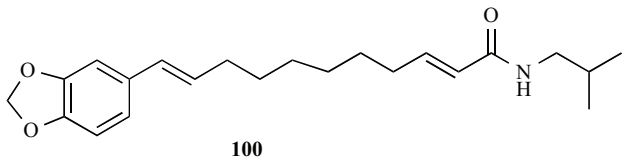
97
Pipernonaline



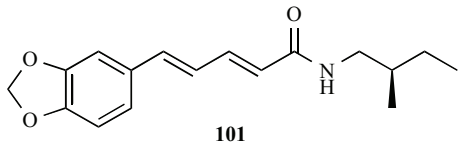
98
Piperchabamide B



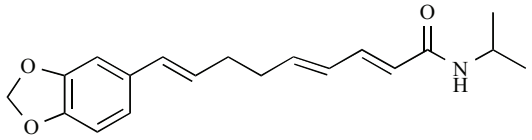
99
Piperchabamide C



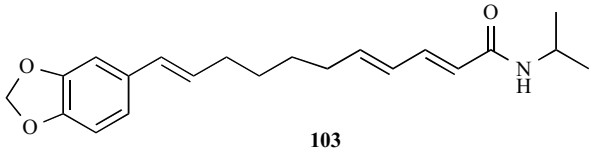
100
Piperchabamide D



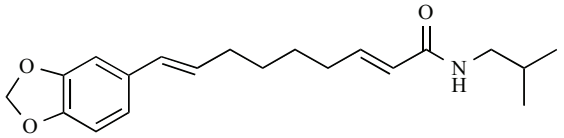
101
Piperchabamide E



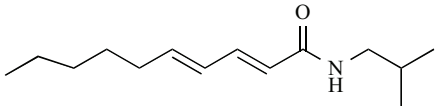
102
Retrofractamide A



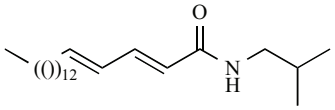
103
Retrofractamide B



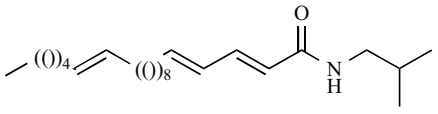
104
Retrofractamide C



105
N-isobutyl-(2E,4E)-decadienamide



106
N-isobutyl-(2E,4E)-dodecadienamide



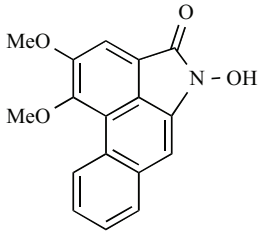
107
N-isobutyl-(2E,4E, 14Z)-eicosatrienamide

4.6. Antioxidant

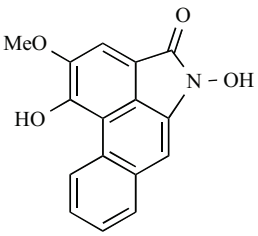
Five alkaloids named piperumbellactams A-D and N-p-coumaroyltyramine were isolated from braches of *Piper umbellatum*. Piperumbellactam A, C and N-p-coumaroyl tyramine were able to scavenge the DPPH radical. The greatest effectiveness of N-*p*-coumaroyltyramine than the

others was possibly due to the presence of its ortho-dihydroxy group which upon donating hydrogen radicals will give higher stability to their radical forms [94].

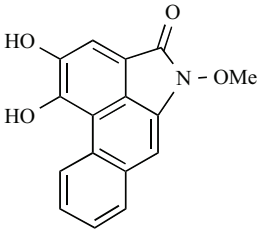
The effect of iperine supplementation significantly improved the erythrocyte antioxidant status in high fat diet and anti-thyroid drug-induced oxidative stress in rats. Simultaneous supplementation with Piperine elevated the antioxidant enzyme activities (SOD, CAT and GPx). This may be because piperine is highly lipophilicinnature and helps inhibiting lipidperoxidation initiated by free radicals, thus preventing or delaying cell damage, and augmenting antioxidant enzymes in tissues of hypercholesterolemic rats. Elevated SOD, CAT and GPx activities in Piperine supplemented animal may also be a consequence of excessive oxidative stress by Piperine in hypercholesterolemic conditions [127]. Moderate and selective α-glucosidase inhibition was observed with piperumbellactams A, B, and C with IC_{50} 98.07, 43.80 and 29.64 μM, respectively [128].



108
Piperumbellactam A

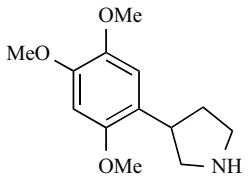


109
Piperumbellactam B



110
Piperumbellactam C

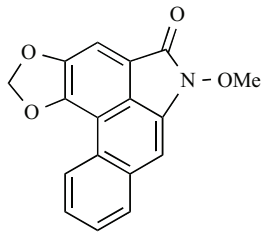
A set of experiments was performed to examine their reactivity towards O_2 using the chemiluminescence technique on sixteen compounds isolated from *Piper cubeba*, among themselves 3-(3',2',5'-trimethoxyphenyl)pyrrolidine and piperine revealed a strong increase in the light emission when they were added to the reaction mixture during the course of the reaction. The enhacemed chemiluminescence from the O_2^--DMSO system shows that these compounds are able to stimulate O2 dismutationand cause the spontaneous dismutation of H_2O_2. The findings mean that compounds showed SOD-like activity, i.e. they were able to delivere H^+ for the reaction producing an emitter of chemiluminescence. In addition, the compounds exhibited at least 20% decreases of the $DPPH^•$ signal demonstrate that most of the compounds tested significantly scavenge HO and DPPH radicals under *in vitro* conditions, thus they can act as antioxidant agents by antiradical mechanism [129].



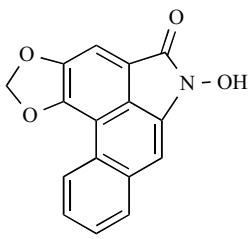
111
3-(3',2',5'-trimethoxyphenyl)pyrrolidine

4.7. Antimicrobial

The inhibitory effects of piperumbellactam D and hydroxyaristolam II from Piper umbellatum on the growth of Trichophyton longifusus, Aspergillus flavus, Microsporum canis, Fusarium solani, Candida albicans and Candida glabrata were examined using *in vitro* diffusion method. The antimicrobial activity is probably due to the ability of meyhylenic carbon in methylenedioxyphenyl to form stable carbine under oxidation [128]. In addition, the water extracts from Piper pulchrum C.D.C. leaves, showed a higher activity against Bacillus cereus and Escherichia coli than gentamycin sulfate. Similarly P. pulchrum presented the lowest MICs against E. coli (0.6 μg/ml) compared to gentamycin sulfate (0.9μg/ml). Likewise, Piper showed an analogous MIC against Candida albicans (0.5 μ/ml, respectively) compared to nystatin (0.6 μg/ml) [130].

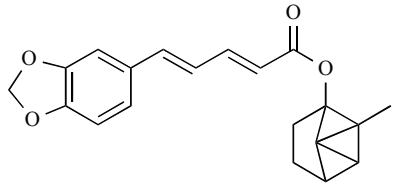


112
Piperumbellactam D



113
Hydroxyaristolam II

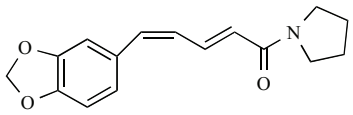
Bornyl piperate, piperlonguminine and piperine were isolated from chloroform extract root of the *Piper chaba.* Bornyl piperate and piperlonguminine, have been found to possess potent antifungal and cytotoxic activities. The compounds have also shown weak antibacterial and antileishmanial activities. Bornyl piperate and piperlonguminine, have demonstrated weak activity against Leishmania donovani promastigotes when compared against standard drug pentamidine [131].



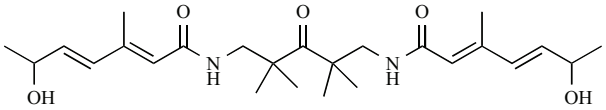
114
Bornyl piperate

Leaves of *Piper arboreum* [132] yielded N-[10-(13,14-methylenedioxyphenyl)-7(E),9(Z)-pentadienoyl]-pyrrolidine (115), arboreumine (116) N-[10-(13,14-methylenedioxyphenyl) -7(E)-pentaenoyl]-pyrrolidine (117) and N-[10-(13,14-methylenedioxyphenyl)-7(E),9(E)-pentadienoyl]-pyrrolidine

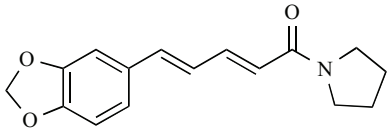
(118). We also have isolated six amides pellitorine, abdihydropiperine (119), piplartine, dihydropiplartine, *cis*-piplartine (120) and fagaramide (121), and two antifungal cinnamoyl derivatives methyl 6,7,8-trimethoxydihydrocinnamate (122) and methyl trans-6,7,8-trimethoxycinnamate (123), from seeds and leaves of *Piper tuberculatum*. Compounds 118 and 119 showed strong antifungal activity, higher than the standards miconazole (0.5 mg) and nystatin (0.5 mg). These two compounds also showed high activity against *C. cladosporioides,* the amide 4 being 50 times more active when compared with the reference compounds. In the case of compounds piplartine, and 120-122, the minimum amount to inhibit the growth of the fungus *C. cladosporioides* on the TLC plates was determined as 5.0 and 10.0 mg, respectively. The higher limit detection of 5 mg values found for pellitorine, 119–120 and 123 indicated a moderate activity of these amides when compared to that observed with the standards miconazole and nystatin. The inhibition of fungal growth displayed for these compounds suggests that the pyrrolidine amides isolated from *P. arboretum* are substantially stronger antifungal agents than the epiperidine, dihydropyridone and isobutyl amides from *P. tuberculatum* [136].



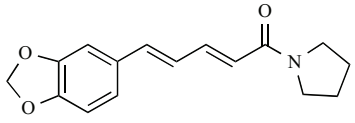
115
N-[10-(13,14-methylenedioxyphenyl)-7(E),9(Z)-pentadienoyl]-pyrrolidine



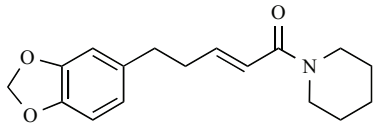
116
Arboreumine



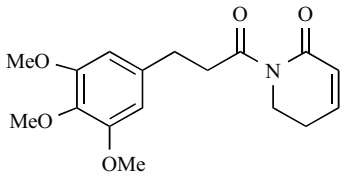
117
N-[10-(13,14-methylenedioxyphenyl)-7(E)-pentaenoyl]-pyrrolidine



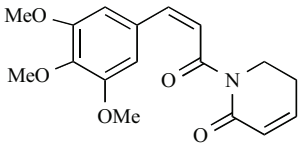
118
N-[10-(13,14-methylenedioxyphenyl)-7(E),9(E)-pentadienoyl]-pyrrolidine



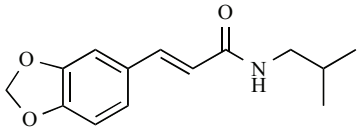
119
Abdihydropiperine



120
Dihydropiplartine



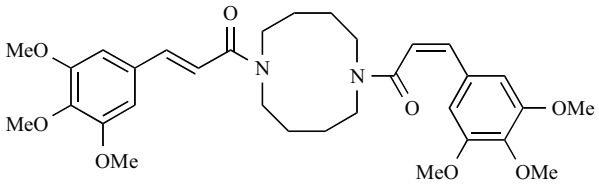
121
***cis*-Piplartine (or 8(Z)-N-(12,13, 14-trimethoxycinnamoyl)-pyridin-2-one)**



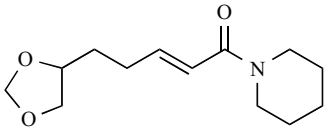
122
Fagaramide

4.8. HIV-1 activity

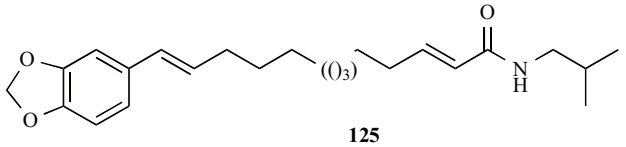
Submultinamide A, pellitorine, dihydropiperine, guineensine, N-feruloyltyramine, N-benzylcinnamide, piperolactam A andaristolactam BII isolated from *Piper submultinerve* were tested employing HIV-1 reverse transcriptase (RT) assay and the syncytium assay. The results indicated that all the tested compounds, except submultinamide A, showed significant anti-HIV-1 activities in the antisyncytium assay. In this assay, pellitorinewas the most active with EC_{50} 35.1 mM and SI 4.7, while guineensine was found very active against HIV-1 RT with IC_{50} 50.8 mM. N-feruloyltyramine, is anti-HIV-1 active in both assays [133].



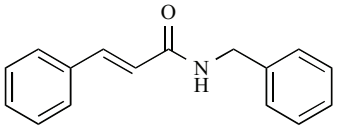
123
Submultinamide A



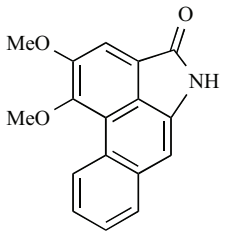
124
Dihydropiperine



125
Guineensine



126
N-benzylcinnamide



127
Aristolactam BII

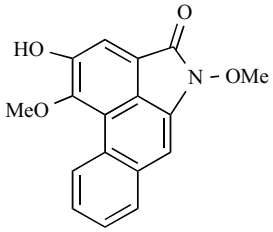
4.9. Anti-Inflammatory

In a study by Bang *et al.*, [134] the efficacy of Piperine as antiathritic was evaluated *in vivo* in a rat model of carrageenan-induced arthritis. The Piperine receiving group (100 mg/kg) showed significant reduction in paw volume. At this dose, Piperines showed almost the same efficacy as prednisolone (10 mg/kg).Piperine also provide a mild antiedema effect at 20 mg/kg, although it was not statistically significant. The vocalizations caused byflexion or extension of the inflamed ankle reached a maximum point on day 1 after thecarrageenan injection and was sustained at a maximum level in untreated rats through the end of the experiment. In the 100 mg/kg piperine treated group, the number of vocalizations started to decrease at 5 days post-carrageenan injection. The group that received piperine has significantly smaller areas of lymphocyte infiltration into the joins compared to the control group.

The molecular mechanismssuggested isthe inhibition of the MAP Kinase activation or IKB kinase signaling pathways. At the maximum concentration tested (100 mg/ml), Piperine slightly inhibited the phosphorylation of ERK1 /2stirnulatedbyIL 1β. Piperine also inhibited the activation of the transcription factor AP-1, but not NFKB, in this system. However, a previous study in B16F-10 melanoma cells showed that piperine was able to inhibit the activation of several transcription factors, includingNFKB, c-FOS, cAMP response element binding (CREB) and activating transcriptionfactor2 (ATF-2). Accordingly, in that study, it significantly reduced the production of IL 1β, tumor necrosis factor (TNF)a, IL6, and granulocyte-macrophage colony stimulating factor (GM-CSF) [135]. These results suggest that piperine has anti-inflammatory, antinociceptive, and antiarthritic effects in an arthritis animal model. Piperine should be further studied with regard to use either as a pharmaceutical or as a dietary supplement for the treatment of arthritis.

In other study Piperine showed significant anti-inflammator activity both in acute and chronic animal models of inflarnmation. Action of Piperine on histamine and formaline-induced inflammation are in support of this observation. It does not acts against adrenolectomized-induced inflammation. This indicates action of piperine on early phases of inflammation mediated through histamine andserotonin but not in later phases of prostaglandin-induced local inflammatory changes [136].

Piper kadsura Ohwiis a medicinal plant that grows in the forest of Taiwan. The stem of *P.kadsura* known as haifengteng, is widely used in the chinese traditional medicine. Alkaloids, piperlactam S and N-p-coumaroy1tyramine were isolated from the stems of *P. kadsura* which showed potent inhibition of phorbol-12-myristate-13-acetate-induced reactive oxygen species (ROS) production in human polymorphonuclear neutrophils [45]. The anti-nociceptiveactivity of the aqueous extract from *Piper sarmentosum*was studied in both the abdominal constriction and hot-plate tests. Moreover, the ability to inhibit both types of stimuli also indicates that the extract possesses a characteristic of strong analgesic with centrally mediated activity [137]. The extract exhibited an opioid-mediated anti-nociceptive effect at the peripheral and central levels based on the ability to inhibit both the abdominals constriction and hot-platetests. COX and prostaglandins inhibitory effects are also suggested at the peripheral and central (as previously reported by Pini *et al.* [138] andUzcátegui *et al*. [139] levels). The extract was also found to decrease the volume of carrageenan-induced paw edema indicating its potential as an anti-inflammatory agent.



128
Piperlactam S

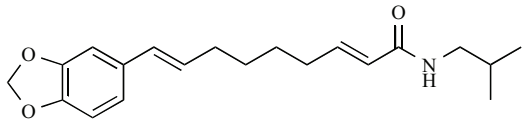
The overall results demonstrate that extracts of *Piper interruptum* Opiz. and *Piper chaba* Linn. have anti-inflammatory, analgesic, and antipyretic activities in experimentalanimals. The results obtained suggest their mechanism of action similar to NSAIDs as well as steroid-like effect [140]. During inflammatory processes, large amounts of the proinflammatory mediator PGE2 are generated by inducible COX-2. PGE2 can affect the immune system by suppressing the proliferation of T and B cells, as well as cytokine synthesis [141]. Piperine significantly inhibited PGE2 production, which is one of the major COX-2 metabolites in RAW 264.7 cells. Furthermore, piperine markedly decreased the gene and protein expression levels of COX-2 expression is primarily regulated at the transcriptional level. Piperine inhibited PMA-induced COX-2 expression by suppressing tran-scriptional factors. Furthermore, piperine inhibited NF-jB, C/EBP and AP-1 transcriptional activity, as shown by transiently expressing the NF-jB, C/EBP and AP-1 reporter in PMA-treated in RAW 264.7 cells [142].

Dendritic cells are also highly responsive to inflammatory cytokines and bacterial products such as

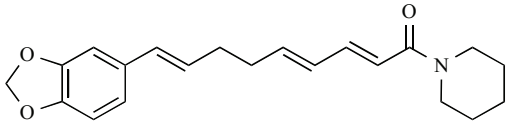
tumour necrosis factor alpha (TNF-a) and lipopolysaccharide (LPS), respectively. These inflammatory mediators induce a series of phenotypic and functional changes in the DCs found in the peripheral organs [143]. Piperine is an inhibitor of DC maturation. Bae *et al.*, [144] provide new insights into the immunopharmacology of piperine, examined the activation of MAPKs in order to investigate the mechanisms through which piperine mediates LPS-induced DC maturation. The MAPKs, including ERK, p38 and JNK subfamilies, are activated in response to stimuli, such as treatment with DNA-damaging agents, growth factors and cytokines [145]. Piperine suppressed the activation of ERK and JNK in LPS-induced DCs. Taken together, these results suggest that piperine suppresses the phenotypic and functional maturation of murine DCs through inhibition of ERK and JNK. Through this mechanism, piperine may provide protection against autoimmune diseases such as arthritis, allergies and diabetes.

4.10. Anti-Obesity

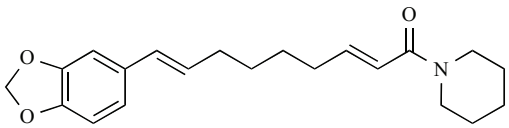
Triglycerides are the main storage form of energy. Excess accumulation in certain tissues leads to serious diseases such obesity, type 2 diabetes and hypertriglyceridemia. Therefore, inhibition of triglyceride synthesis represents a potential therapeutic for obesity. Bioassay-guided isolation of $CHCl_3$ extracts of the fruits of *Piper longum* and *Piper nigum* using an *in vitro* acyl CoA:diacylglycerol, acyltransferase(DGAT) inhibitory assay lead to isolation of an alkamide named (2E,4Z,8E)-N-[9-(3,4-methylenedioxyphenyl)-2,4,8-nonatrienoyl]-piperidine, retrofractamide C, pipernonaline, and piperrolein B. These compounds possessing piperidine groups can be potential DGAT inhibitors [146].



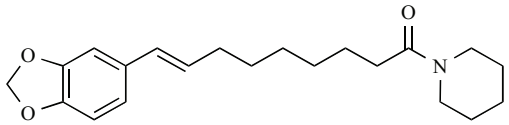
129
(2E,4Z,8E)-N-[9-(3,4-methylenedioxyphenyl)-2,4,8-nonatrienoyl]- piperidine



130
Retrofractamide C



131
Pipermonaline



132
Piperrolein B

Piperine's ability to inhibit drug metabolism when its administration to rats increased the oral bioavailability of the alkaloids sparteine and vasicine by factors of two and three, respectively [147]. Follow-up studies observed that piperine administration was a noncompetitive inhibitor of various murine hepatic monoxygenases as well as UGTs [148]. Subsequent studies confirmed Piperine's inhibitory effect on UGTs is more pronounced in intestinal epithelial cells than hepatocytes [149]. Moreover, structure-activity relationship studies involving more than 35 separate analogues revealed that piperine is especially suited for CYP inhibition [150]. Modifications to either the MDP moiety or piperidine side chain significantly reduced its potency [151]. In addition to its inhibitory effects on XMEs and ABCB1, piperine may also promote drug absorption by modulating the permeability characteristics of intestinal membranes as well as through stimulating increases in microvilli length. One of the most compelling aspects of piperine is its ability to dramatically enhance the oral absorption of concomitantly administered medications [152]. Recognizing piperine s utility as a bioavailability enhancer, many dietary supplement manufacturers incorporate *P. nigrum* or *P. longum* extracts into botanical formulations as a means of improving phytochemical efficacy.

4.11. Cardiovascular

Piperdardine isolated from *Piper tuberculatum* Jacq. produced a decrease in diastolic blood pressure followed by a significant decrease in heart rate, probably due to a direct cardiac depressant effect and as a result of a direct spasmolytic effect diastolic blood. Intravenous injection of piperdardinein normotensive rats reduced the diastolic blood pressure (DBP) and heart hate (HR) in a dose dependent manner. This effect was affected in rats treated with methysergide, an inespecific serotonergic antagonist. In anesthetized and ventilated animals, piperdardine lowered the DBP and the HR in a significative manner. However, these effects were completely abolished after bilateral cervical vagotomy. The piperdardine relaxed phenylephrine or KCl pre-contracted rat aortic artery rings both with intact or denuded endothelium. These results taken together, suggest that the hypotension and bradicardia observed after piperdardine isprobably due to direct cardiac activation and as a result ofa direct spasmolytic effect [153].

Piperine has none direct effect on the heart, although it exhibited positive chronotropic and inotropic effects mediated through the release of calcitonin gene-related peptide from non adrenergic and noncholinergic nerves in isolated rat atria. Piperine is different from verapamil, with a vasoconstrictor effect possibly mediated through Ca^{2+} release, which may offer therapeutic merit by not allowing BP to decrease beyond a certain limit and which also supports the general belief that food remedies are mild to moderately effective with lesser side effects [153]. Intravenously administered of *Piper betle* aqueous extract induced depression and bradycardiac responses that could be reversed or inhibited by atropine and vagotomy, revealing that a parasympathetic different pathway is involved in the action of *P. betle* [154].

4.12. Neuropharmacological

Piperovatine was isolated from *Piper piscatorum,* it induced intracellular calcium flux which was eliminated in the presence of the voltage-gated sodium channel blocker (TTX). The suppression of increases in intracellular calcium induced by TTX, eliminates the possibility that this could be a direct result of intracellular calcium store release but does notindicate a direct causative role of the voltage-gatedsodium channels. TTX would successfully suppress any calcium increase mediated directly or not by voltage-gated sodium channels. Binding studies using radiolabeled batrachotoxin (BTX), have indicated that synthetic N-alkylamides, similar in structure to piperovatine, N-isobutyl-phenyl-2E,4E-hexadieneamide and *N*-isobutyl-phenyl-2E,4E-heptadieneamide bind with high affinity at site 2, the BTX and veratridine binding site, of mouse brainvoltage-gated sodium channels. The isobutyl amide, piperovatine, is shown to be a potent stimulator of neuronal intracellular calcium increase. This effect was blocked by the voltage-gated sodium channel antagonist, TTX, but was not measurably affected by the mAchR antagonist, atropine, indicating that sodium channels, not mAchRs, are implicated in its mechanism of action. The exact nature of piperovatine interaction with the sodium channel could not be ascertained in these experiments due to limitations of the functional assay employed. It is certain that piperovatine produces marked increases in neuronal intracellular calcium, similar in duration and character to other voltage-gated sodium channels agonist [155].

4.13. Cognitive Disorders

Recently, numerous medicinal plants possessing profound central nervous system effects and antioxidant activity have received much attention as food supplement to improve cognitive function against cognitive deficit condition including in Alzheimer's disease condition. The number of patients suffering from Alzheimer's disease (AD) condition all over the world is rising continually and becomes one of the biggest challenge for most societies throughout the world [156]. It is characterized by irreversible, progressive loss of memory followed by complete dementia [157]. Piperidine demonstrated that significantly improved spatial memory and neurodegeneration. Therefore, data suggested that the cognitive enhancing effect of piperine might occur partly via the cytoprotective effect and the inhibition of AChE in hippocampus. However, it was found that Piperine, especially at low dose, could increase the density of neurons in hippocampus more than those in naïve intact control. Therefore, the increased neuron density in hippocampus might involve its neurotrophic action [158].

Piperine, has been investigated on rats after the intracerebroventricular administration of ethylcholine aziridinium ion (AF64A) bilaterally. The results showed that Piperine at all dosage range used in this study significantly improved memory impairment and neurodegeneration in hippocampus. The possible underlying mechanisms might be partly associated with the decrease in lipid peroxidation and acetylcholinesterase enzyme. Moreover, Piperine also demonstrated the neurotrophic effect in hippocampus [159].

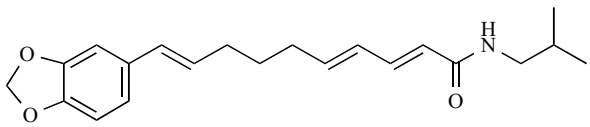
Other study focused on the anti-depressive activity of Piperine and cognitive enhancing effect at low doses. They found that at doses of 10 mg/kg for 30 days there was a toxic effect on male reproductive system. Still at low doses is a potential alternative to improve brain function [160].

4.14. Larvicidal

Diseases that are transmitted by insects, remains a major source of morbidity and mortality worldwide. Mosquito vectored pathogens infect more than 700 million people annually around the world through diseases such as malaria, filariasis, dengue, yellow fever, Rift valley fever and Japanese encephalitis. Malaria alone kills 3 million people each year. Although mosquito-borne diseases currently represent a greater health problem in tropical and sub-tropical climates, no part of the word is immune to this risk. Control of such diseases is becoming increasingly difficult because of increasing resistance of mosquitoes to insecticides [43].

The crude aqueous extract of dried fruits of *P. nigrum*has been found to possess a larvicidal effect against the IV larval instars of the mosquito *Cx. quinquefasciatus.* Some of the piper species, *P. longum, P. guanacastensis* and their bioactive constituents are reported to have remarkable larvicidal activity against various mosquitospecies suchas *Cx. pipiens pallens, Ae. aegypti, Ae. Togoi*and *Ae. atropalpus*. Variety of type of active constituents aspipernoneline, piperidine, methyl-4-hydroxyl-3-(3'-methyl-2' butenyl)benzoate in the piper species maybe responsible for the variability in their potential against *Cx. quinquefasciatus* larvae [161].

A different study reports that alkaloids isolated from the fruits of *P. nigrum* act as insecticidal principle. After 48 h of treatment the LC_{50} values were obtained, the most toxic compound for *C. pipienspallens* larvae, was pipercide (0.004 ppm) followed by retrofractamide A (0.028 ppm), guineensine (0.17 ppm), and pellitorine (0.86 ppm). Piperine (3.21 ppm) was least toxic against *A. aegypti* larvae, larvicidal activity was more pronounced in retrofractamide A (0.039 ppm) than in Pipercide (0.1 ppm), guineensine (0.89 ppm), and pellitorine (0.92 ppm). Piperine (5.1 ppm) was relatively ineffective against *A. togoi* larvae, retrofractamide A (0.01 ppm) was much more effective, compared with pipercide (0.26 ppm), pellitorine (0.71 ppm), and guineensine (0.75 ppm). Again, very low activity was observed with Piperine (4.6 ppm). Structure-activity relationships indicate that the N-isobutylamine moiety might play a crucial rolein the larvicidal activity, but the methylenedioxyphenyl moiety does not appear essential for toxicity [162].



133
Pipercide

Insecticidal constituents of *Piper* fruits were reported to be: N-isobutylamide alkaloids such as dihydropipercide, guineensine, pellitorine, and pipercide. These isobutylamides

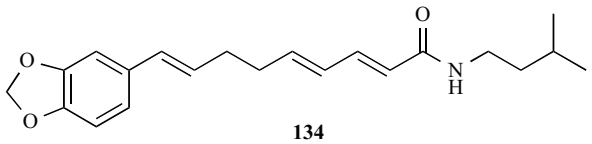
are very good at knocking down adults of C. *chinensis, M. domestica,* and *Periplaneta americana.* Lethal activity of Pellitorine against *M. domestica* adults ishalf of that of pyrethrins. Bioactivity against C. *chinensis* adults is high, in the order of dihydropipercide, guineensine, and pipercide [163]. Su and Horvat [164], also reported guineensine, pellitorine, and pipercide as insecticidal constituents from *P. nigrum* fruits against adults of S. *oryzae* and C. *maculatus:* the order of lethal effect was pipercide>guineensine> pe1litorine. Electrophysiological investigations have shown that pipercide induced only repetitive discharge on the exposed central nerve cord of *P. americana*adult males, but pyrethrin induced repetitive discharge as well as conduction blockage on the exposed central nerve cord.

Miyakado *et al*., [165] studied the toxic effects of thecompoundsbychangingtheamide moiety from the isobutylarnine of dihydropipercide to other branched or cyclic aliphatic amines: insecticidal activity of these synthetic amines was decreased by one-third or one-fourth compared with that of the parent dihydropipercide. Steric limitation on the size of the amine wassuggested to be relate with insecticidal activity. Structural modification studies on the effect of aromatic ring substituents on insecticidal activity have shown that the 3,4-methylenedioxyphenyl group does not appear essential for toxicity. However, the introduction of a phenyl ring has improved its chemical stability [166].

Piper retrofractum Vahl (Piperaceae), showed the highest level of activity against mosquito larvae. Fresh fruits of this plant were extracted in water and the extracts were bioassayed against 3rd and 4th instar larvae of *C. quinquefasciatus* and *A. aegyptiy.* Extracts of unripe (001/3) and ripe (002/3 and 001/4) fruits showed different levels of activity against *C. quinquefasciatus* larvae. The ripe fruit extract 002/3 was some what more active against *A. aegypti* than *C.quinquefasciatus*. Another ripe fruit extract (001/4) was much more toxic to both mosquito species. Diluted solutions of the solid extract (002/3) in distilled water lost their larvicidal activity upon aging [166]. In addition, methanol extract of *Piper longum*who was found to be active against the larvae of *Aedes aegypti*, was subjected to an activity-guided isolation to yield pipemonaline that is the insecticidal compound [167].

It is very important to monitor the insecticide susceptibility status of mosquito vectors at different areas in view of the resurgence of various communicable diseases. Literature survey has revealed bioassay experiments for exploring the insecticidal activity on mosquito vectors from many piper species. But most of the studies with piper species on mosquitoes are concentrated on *P.nigrum,* the common pepper [168]. However, considerable works have also been done with several other plants of the same species. For instance, three plants namely *P. logum, P. ribesoides* and *P. sarmentosurri* have shown adulticidal activity against *Stegomyia aegypti* at Thailand [169].

Bioassaysguided fractionated from petroleum ether extract from fruits of *Piper longum*lead to isolationof a larvicideamide, pipyahyine [170], which have activity on *Culex quinquefasciatus* and *C. quinquefasciatus* with LC_{50} of 0.58 and 1.88 ppm respectively.



134
Pipyahyine

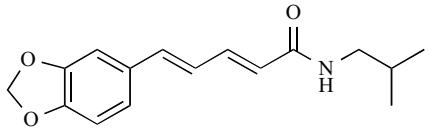
The northern house mosquito, *Culex pipiens pallens* (Coquillett), and the yellow fever mosquito, *Aedes aegypti* (L.), are widespread and serious disease vectoring insect pests. Plants may be an alternative source of mosquito control agents because they constitute a rich source of bioactive chemicals. Phytochemistry, insecticidal activity and mode of action of *Piper* spp. have been well discussed by Scott *et al.* [170]. In other report describes a laboratory study in which examined the insecticidal activity of *Piper nigrum* fruit-derived piperidine alkaloid and N-isobutylamide alkaloids (piperine, pellitorine, guineensine, pipercide, retrofractamide A) against female adults of *C. pipiens pallens* and *A. aegypti*. Based on 24-h LD_{50} values, the compound most toxic to *C. pipiens pallens* female adults was pellitorine (0.4 μg) followed by, guineensine (1.9 μg), retrofractamide A (2.4 μg) and pipercide (3.2 μg). LD_{50} value of piperine was 45 μg. In a test with *A. aegypti*, pellitorine showed the strongest adulticidal activity (0.17 μg). The toxicity of guineensine (1.7 μg) and retrofractamide A (1.5 μg) was similar. Pipercide (2.0 μg) was least toxic. LD50 value of piperine was 45 μg. N-isobutylamide alkaloids exhibited the potent insecticidal activity against adult females of *C. pipiens pallens* and *A. aegypti* [171]. However, piperine was relatively ineffective against mosquito adult. Isobutylamine moiety appears to be essential for the insecticidal activity against mosquito adult. Additionally, there was a difference in the adulticidal activity between the isobutylamides with and without a methylenedioxyphenyl moiety. The adulticidal activity of pellitorine was more potent than guineensine, pipercide and retrofractamide A, the latter three being equitoxic. Hatakoshi *et al.* [172] reported that pipercide did not show knockdown activity owing to its slow penetration but exhibited knockdown activity when a proper amount of pipercide existed in the insect body. On the basis of similar chemical structures of pipercide, guineensine and retrofractamide A, it can be presumed that guineensine and retrofractamide A also have a slow penetration rate. Pellitorine might have notable toxicity and more rapid penetration rate than methylendioxyphenyl-containing amides on mosquito and fly adult. However, the larvicidal activity of isobutylamides with a methylenedioxyphenyl moiety such as retrofractamide A, pipercide and guineensine was stronger than that of pellitorine against mosquito larvae [173].

4.15. Antihyperlipidemic

Cholesterol and lipids such as phospholipids and triglycerides (TG) play critical roles in the maintenance of internal homeostasis of the organisms and the histological organization and intermediary metabolism of eukaryotes. However, abnormalities in lipid metabolism are attributed to many disease states, including atherosclerosis, which is

a main nosogenesis of many cardiovascular and cerebrovascular disorders [174].

Blood lipid levels in rats with hyperlipidemia resulting from high-fat feeding were determined after oral administration of alcoholic extract of the fruit of *Piper longum* L. Administration of the extract produced a significant decrease of blood triglyceride, total cholesterol and LDL-cholesterol levels. What is more, HDL-cholesterol level was significantly increased. A bioassay-guided isolation of an ethanol extract of the fruit of *Piper longum* L. yielded piperlonguminine, piperine and pipemonaline, as the main antibyperlipidemic constituents. They exhibit appreciable antihyperlipidemic activity *in vivo,* which is comparable to that of the commercial antihyperlipidemic drug, simvastatin [175]. Treatment with Piperine derivative (GB-N) on RT-PCR analysis significantly increase levels of LCAT mRNA, while western blotting analysis also revealed significant increases in the protein expression of LCAT. The hyperlipidemic rats treated with GB-N also had a significant increase in the level of HMG-CoA mRNA. GB-N could significantly increase the levels of LCAT mRNA and protein expression. LCAT is an important enzyme for HDL metabolism, which catalyzes the free cholesterol into esterification. Gene mutation at LCAT markedly reduces HDL-C level in humans [176]. On the other hand, hyperlipidemia downregulates the LCAT mRNA level and decreases the activity of LCAT in blood plasma, which impairs the capability of HDL-C to remove cholesterol and leads to cholesterol accumulation in the blood.



135
GB-N

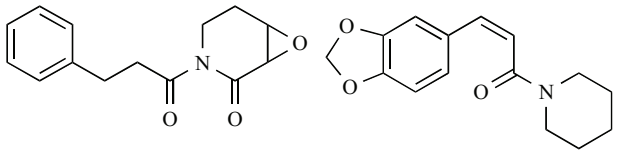
4.16. Antiplasmodial

The leishmaniasis includes a group of tropical diseases with considerable morbidity and mortality rates in most developing countries. A broad spectrum of clinical manifestations, ranging from asymptomatic to cutaneous, mucocutaneous, and visceral leishmaniasis is recognised. Cutaneous leishmaniasis is mainly caused by Leishmania major in the Old World and by *Leishmania amazonensis* and *Leishmania braziliensis* in the Americas particularly in Brazil [177].

The antiplasmodial activity of antiepilepsirine and kaousine from *P. capense* were evaluated *in vitro* against the chloroquine-resistant strain W2 of *Plasmodium falciparum*. Lower activity was observed for kaousine (lC_{50}= 20 µg/ml), whereas antiepilepsirine demonstrated high activity that the chloromethylenic extract of *P. capense* (lC_{50}= 7 µg/ml) [178]. In other report the crude methanol extract of *P. betle* demonstrated significant schizonticidal activity in models of the antimalarial evaluations [179].

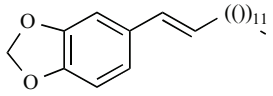
The antiplasmodial activity of the purified compounds was evaluated *in vitro* against the chloroquine-resistant strain W2 of *Plasmodium falciparum*. Lower aectivity was observed for Kaousine (lC_{50} = 20 µg/ml), whereas antiepilepsirine demonstrated the same activity that the chloromethylenic extract of *P. capense* (lC_{50} = 7 µg/ml). In other report. The crude methanol extract of *P. betle* demonstrated significant schizonticidal activity in models of the antimalarial evaluations [180].

Ghosal *et al*., [181] isolated seven compounds with leishmanicidal activity against promastigotes and axenic amastigotes of *Leishmania donovani* from *P. longum*. 138 is the most potent compound with an IC_{50} value of 9 µg/mL (19.2 µM) and 2.81 µg/mL (5.9 µM), respectively. Interestingly, they all displayed significantly higher activity against the amastigotes compared to promastigotes. Cell cytotoxicity measured at IC_{50} concentration and twice the concentration of the IC_{50} showed that none of the compounds exhibited more than 7.5% cytotoxicity. An analysis of the all structures revealed that compounds containing a longer aliphatic linking chain displayed higher activity in comparison to a shorter alkyl chain. However, compounds containing a monoenamide (140, 142), dienamide (141, 143), or methylenedioxy phenyl moiety (139) attached to a long aliphatic chain displayed almost similar activity. A number of synthetic amides related to piperlongumide may provide further insight in designing more.

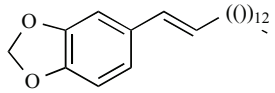


136
Kaousine

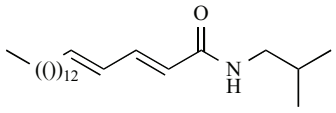
137
Antiepilepsirine



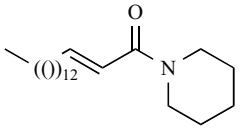
138
1-(3,4-methylenedioxyphenyl)-1E-tetradecene



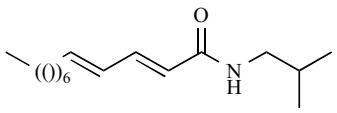
139
Piperlongimin A[2E-N-isobutyl- hexadecenamide]



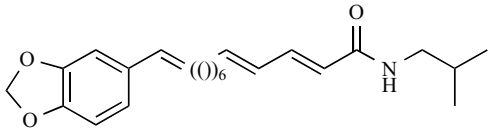
140
2E,4E-N-isobutyl-octadecenamide



141
Piperlongimin B [2Eoctadecenoylpiperidine]

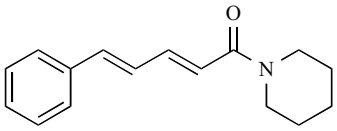


142
2E,4E-N-isobutyl-dodecenamide



143
2E,4E,12E,13-(3,4-methylenedioxyphenyl)-trideca- trienoic acid isobutyl amide

It was also reported in another study that the Piperine and phenylamide were selectively toxic to the mitochondria in *Leishmania*, since cells with damaged mitochondria were unable to metabolize XTT to a water-soluble formazan dye [182]. These results thus showed that treatment with 15 μM and 50 μM piperine inhibited the parasite's viability in 36% and 64%, respectively. Phenylamide at 25 μM and 50 μM also reduced the promastigotes viability in by 58% and 64%, respectively, when compared to untreated cells.



144
Phenylamide

5. CLINICAL STUDIES

5.1. Drug interactions

Recently, several reports have demonstrated that natural compounds and herbal products maycause pharmacokinetic interaction with western drugs used clinically when they are simultaneously administrated [183]. Piperine is also known to enhance the bioavailability of some drugs by inhibiting drug metabolism or by increasing absorption. Thus, piperine may prove to be useful on combination treatments with other drugs. For example, a combination of gallic acid and piperine reduced beryllium-induced hepatorenal dysfunction and the associated oxidative stress [184]. In addition, a synergistic effect of piperine was demonstrated in a clinical study that tested the pharmacokinetics of nevirapine, a potent non-nucleoside inhibitor of HIV-1 reverse transcriptase [185]. The combination therapy was well tolerated, with few or no clinical adverse effects, and the mean maximum plasma concentration of nevirapine was increased when combined with piperine. In another clinical study, piperine was shown to increase the plasma levels of coenzyme Q10 [186]. Therefore, Piperine may improve the therapeutict or lower the dose requirements of other drugs when administrated with antirheumatic drugs (DMARDs) as a therapeutic drug or dietary supplement. In addition, combinations of DMARDs with piperine may reduce the side effects of DMARDs. The bioavailability-enhancing property of Piperine indicates its potential to be used as an adjuvant with therapeutic drugs in chronic ailments, to reduce the effective dose of the drug and, hence, subsequent adverse effects.

The influence of Piperine on kinetic profiles of propranolol and theophylline has been studied. A major kinetic problem with propranolol is its high first pass metabolism and consequent poorsystemicavailability. Sharp peaks and troughs in the steady state levelsand sbort dosing intervals also contribute poor therapeutic control in theophyllinc therapy, any pharmacological intervention that enhanced the bioavailability of either drug and produced sustained levels for a longer period should be advantageous. The effect of piperine on the bioavailability and pharmacokinetics of propranolol and theophylline has been examined in a crossover study. Six subjects in each group received a single oral dose of propranolol 40 mg or theophylline (150 mg) alone or in combination with piperine 20 mg daily for 7 days. An earlier $t_{max}$and a higher $C_{max}$and the are a under the serum concentration-time curve (AUC) were observed in the subjects who received piperine and propranolol. It produced a higber C_{max}, longer elimination half-life and a higher AUC with the ophylline. In clinical practice, the enhanced systemica vailability of oral propranolol and theophylline could be exploited to achieve better therapeutic control and improved patient compliance [187].

Resveratrol is a phytoalexin shown to possess a multitude of health-promoting properties in pre-clinical studies. However, the poor *in vivo* bioavailability of resveratrol duet oits rapid metabolism is being considered as a major obstacle intranslating its effects in humans. In this study, Piperine was examined to test if it would enhance the pharmacokinetic parameters ofresveratrol. The result was positive, and it could be via inhibiting its glucuronidation, thereby slowing its elimination. So Piperine significantly improves the *in vivo* bioavailability of resveratrol [188]. Pharmacokinetics of phenytoin was studied in healthy subjects. In a cross-over study five volunteers received either a simple dose (300 mg) of phenytoin aloneorin combination with multiple doses of piperine (20 mg X 7 days). A single dose of piperine for 7 days decreased the absorption halflife in comparation to phenytoinal alone altering the pharmacokineties parameters of the antiepileptic phenytoin [189].

CONCLUSION

The pharmacological studies conducted on *Piper* indicate the immense potential of this plant in the treatment of conditions such as cancer, anti-depression, hepatoprotection, antimicrobial, anti-obesity, neuropharmacological, cognitive disorders, antihyperlipidemic, antifeedant, cardioactive, immuno-enhancing, etc. Not surprisingly, *Piper* also exhibits antioxidant and anti-inflammatory effects as oxidative injury underlies many of these diseases. However, the diverse pharmacological activities of *Piper* extracts and isolated phytochemicals have only been assayed in *in vitro* tests using laboratory animals, and the results obtained may not necessarily be those observed in humans. While there are gaps in the studies conducted so far, which need to be bridged in order to exploit the full medicinal potential of *Piper*, it is still very clear that it is a family of plants with an

already tremendous widespread and with an extraordinary potential for the future. Further research, clinical trials and product development can cement *Piper* as a very important part of our biodiversity to respect and sustainably use for generations to come.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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