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Black Pepper, the "King of Spices": Chemical composition to applications

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Abstract

This article brings together an overview of the historical and scientific works on black pepper (BP). It's well known as the king of spices, and literature which is very rich showing that it was well cultivated tens of centuries ago before the birth of Christ. It was known first in India but its economic importance as well as medical uses extended to several countries. The ancient books illustrated the displacements of caravans of merchants known as route of Silks and Spices. Actually, the countries of India, Brazil, and Indonesia are the greatest commercial exporters. The major compound of black pepper is piperine that imparts pungency and biting taste to it. Hundreds of millions of results on black pepper on Google reflects the importance of this naturally occurring alkaloid. The numerous health effects and beneficial therapeutic properties have been largely demonstrated. The chemical composition of BP is so various to find heterocyclic components, and mineral ions as potassium, calcium, magnesium, iron … Advanced extraction and quick characterization yield these numerous alkaloids based on piperine. Also, the development of new formulations improves its in vivo bioavailability and explains the multiple uses of this "King" of spices in the medicinal applications. Black pepper and its isolated compounds served also as efficient corrosion of mild steel in acidic media

Keywords: Black Pepper, Piperine, Alkaloid; Medical uses.

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1. Introduction

Piper nigrum, is called as black pepper and known as the "King" of spices, is a member of the family piperaceae. The fruit of Piper nigrum, also called as pepper is an ancient and famous spice throughout the world. Piper nigrum is a native of Malabar seashore of India and has its utility as a redolent stimulant in cholera, flatulence, arthritis disease, gastrointestinal disorders in livestock, dyspepsia and anti-periodic in malarial fever. Piper nigrum is the familiar species of genus piper because of its high economic, commercial and medicinal values. The genus piper is having a rich phytochemistry and researchers showed the ample presence of alkaloids, amides and terpenoids [1-10]. The various pharmacological activities of Piper nigrum are radical scavenging, antioxidant, anti-insecticidal, allelopathy, anticonvulsant, anti-inflammatory, anti-tubercular, antibacterial, antipyretic, exterofective and antioxidant. This large climbing liana (up to 20 m in length) of evergreen forests in southwest India, black pepper (*Piper nigrum*), a perennial crop of the tropics belongs to *Piperaceae* family [3-7] as grouped below :

Kingdom	Division	Class	Order	Family	Genus	Species
Plantae	Manoliophyta	Magnoliopsida	Piperales	Piperaceae	Piper	nigram

Literature reported the genus Piper contains more than 1000 species [8-12]. *P. nigrum* has different common names according to its location and languages. Its common name in English is pepper, in

Urdu (kali mirch), in Indonesian (Lada Hitam), in Vietnamese (Tiêu đen), in Greek (pipe´ri), in Chinese (hujiao), in French (poivre commun), filfil (فلفل أسود) in Arabic, pfeffer in German and pimienta in Spanish. Figure 1 shows the Evolution of BP from tree to be collected and dried. We cannot imagine houses and restaurants without black pepper; consequently, high demand for nutrients and medical uses was imposed during centuries. As a conclusive remark, *P. nigrum* should not only be regarded as “King of spices” but can also be considered as part of the kingdom of medicinal agents, comprising a panoply of bioactive compounds with potential nutraceutical and pharmaceutical applications.

Figure 1: Black Pepper : from tree to collect

2. History

Researchers pointed out that black pepper marked the history of humankind that the mummy of Ramesses II of ancient Egypt, dating back at least as early as 13th century BCE, contained black pepper [13-17]. Moreover, Ahmad in his book, advanced that nearly 3000 years before the birth of Christ, both Babylonians and Assyrians were trading in spices, primarily black pepper, with the people of the Malabar coast in the state of Kerala on the Indian subcontinent [18].

P. *nigrum*, native to India, requires high temperatures with heavy and frequent rainfalls and well-draining soil for optimum growth [14, 19-21]. These plants cannot tolerate frost. These conditions are usually met in the countries of India, Brazil, and Indonesia, so these are the greatest commercial exporters of peppercorns [21, 22].

3. The World's Top Black Pepper Producing Countries

There is hardly any city or village in India devoid of a market for the sale of spices, which are considered one of the most prevalent foodstuffs in the country, and it is even said that the name spice in Arabic Bharat (بهارات) is derived from the ancient name of India Bharat. Also, the prices and amount of spices were considered in the past, an indication of the growth or decline of the economy in the country. Near silks and spices demand by various populations in continents, West and east Asia was connected to middle east, Africa and Europe via the known silk and spices Road [23]. Several ways were cited in literature as China to Rome road along with horses in exchange for wool, gold, and silver coming in from the Europe via the Mediterranean Sea [24] or via Tombouctou (or Timbuktu) as well as the South Africa [25, 26]. This route, illustrated in Figure 2, was mainly maritime or camel route used by many countries to trade spices [26, 27]. The availability of spices like cinnamon, cassia, cardamom, ginger, pepper, nutmeg, cloves was rare in the west. These commodities were highly sought after. Before the 15th century, the whole market of spices was controlled by the Arabs and the North African men which made them extremely costly. With the advent of the Age of Exploration sailing, long distances became possible and Europeans used this opportunity to forge economic relations with the east. This made the middlemen useless and the availability of spices easy and cheap [28]. The main mode of transportation used was the camel. Camel was domesticated (Figure 3) around 1000 BCE [29]. This allowed the Arabs to export frankincense and myrrh. These became the most valued commodity for the Romans, the Greeks, and the Egyptians. The trade flourished and at its height, the route saw 3000 tons of incense trading. The root cause of the decline of the route was the discovery of shorter and cheaper sea routes that made trading more efficient.

Figure 2: Silks and Spices Route [28]

The analyses of Frankopan [31] and Hansen [32] show that the history of the 7000-km long trade route, known as the Silk Road dated around 1500-year-old trade corridor. Currently, its leading producer is Vietnam, which produces 34% of the world-wide production of 470,000 metric ton [30,33]. Vietnam is the world leader in the production of black pepper, producing 163,000 tons which are about 34%

of the world's production. The plant is a traditional cash crop in the country, and 95% of the black pepper produced is for export primarily to the US, India, the Netherlands, and Germany. Indonesia is the second largest producer at 89,000 tons while India produces 53,000 tons. Top black pepper-producing regions in India are Kerala, Karnataka, Konkan and Tamil Nadu. Other countries on the list are Brazil (42,000 tons) and China (31,000) [34]. Distribution of BP production is presented in Figure 4.

Figure 3: Relief with camel, Persepolis, Iran. Image courtesy Wikimedia Commons [28, 30]

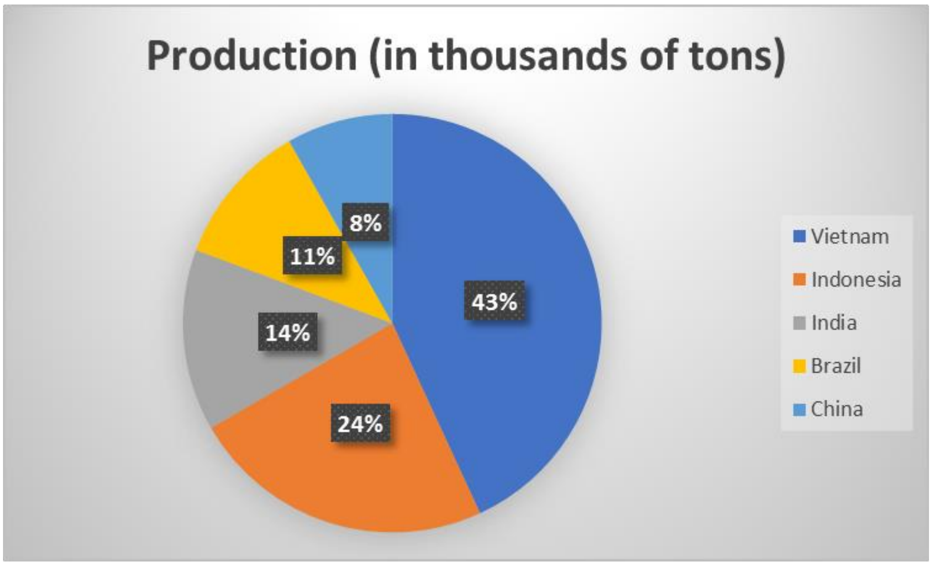


Figure 4: The World's Top Black Pepper Producing Countries by Benjamin Elisha Sawe on June 7 2019 in Economics [35]

The "King" of spices, black pepper (*Piper nigrum* L.) and the "Queen" of spices, cardamom (Elettaria cardamomum M.), both perennial crops of the tropics, are the most important and most widely sought-after spice crops of the world (Figure 5). Black pepper was once one of the most traded spices worldwide, often referred to as “black gold” because it was used as currency throughout the commercial routes between Europe and India [36].

We have shown that the production of different spices during time created spontaneously an economic business between productive and imported countries. The Global Market increased significantly, as we observe with Coffee, rice, exotic fruits etc… (Figure 6). Whether organic agriculture combined with fair trade marketing systems can mutually strengthen and benefit smallholder farmers in emerging economies have significant income gains they were able to add to their wealth [36-40].

Black pepper (Piper nigrum L.) Cardamom (Elettaria cardamomum M.)

Figure 5: The King and Queen of Spices

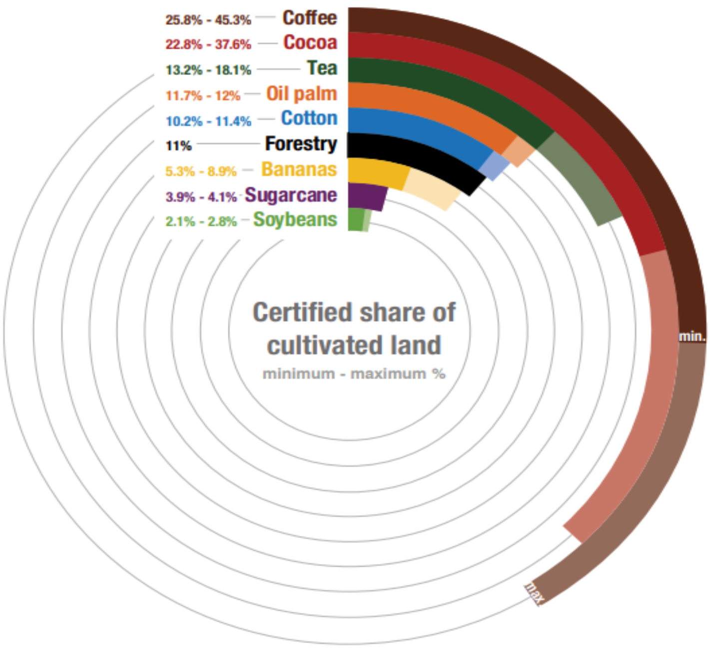


Figure 6: Global Market of agriculture [33].

CATR (Center of Advance Trade Research) [36], reported that India, stays the home of spices since a long trading history with ancient and medieval civilizations of the world. Ancient trade routes connected India with Europe, Middle East and the rest of the world exists as a testimony to world’s preference for

Indian spices since ancient times. Indian spices are known for its exquisite aroma and medicinal properties. Moreover, India has the world's largest domestic market for spices. Presently, India is the world's largest producer, consumer and exporter of spices. It produces about 75 of the 109 varieties of spices listed by the International Organization for Standardization (ISO) and accounts for half of the global trading in spices. Top spices produced in India include pepper, cardamom, chilli, ginger, turmeric, coriander, cumin and others. Kerala is the topmost spice producing state in India and is also the largest producer of Pepper and Cardamom. The top importers of Indian spices in 2017 were: Vietnam, USA, Malaysia, Thailand, Sri Lanka, UAE and UK. India has remained the topmost world exporter of spices throughout, followed by Vietnam and China. The top imported spices in the world in 2017 were Whole Pepper (USD 2.2 billion) and Capsicum (USD 1 billion). India was the fifth largest exporter of Whole Pepper in 2017 [36].

4. Chemical composition of Black Pepper

Since black pepper has been used in both cooking and traditional medicine to cure constipation, toothaches, oral abscesses, and sunburn, among others [40], it is evident that it receives more attention to researchers and herbal users. Studies show that these properties of BP are mainly due to this pungent alkaloid called piperine and its structural analogues [41-63]. Piperine (Figure 7) isolated firstly from the extract of pepper by Hans Christian Ørsted in 1819 [64]. It was extracted as a yellow crystalline compound with a melting point of 128 to 130 °C. The study of degradation of piperine, flavour of BP was widely studied for various applications in medical uses [65-78].

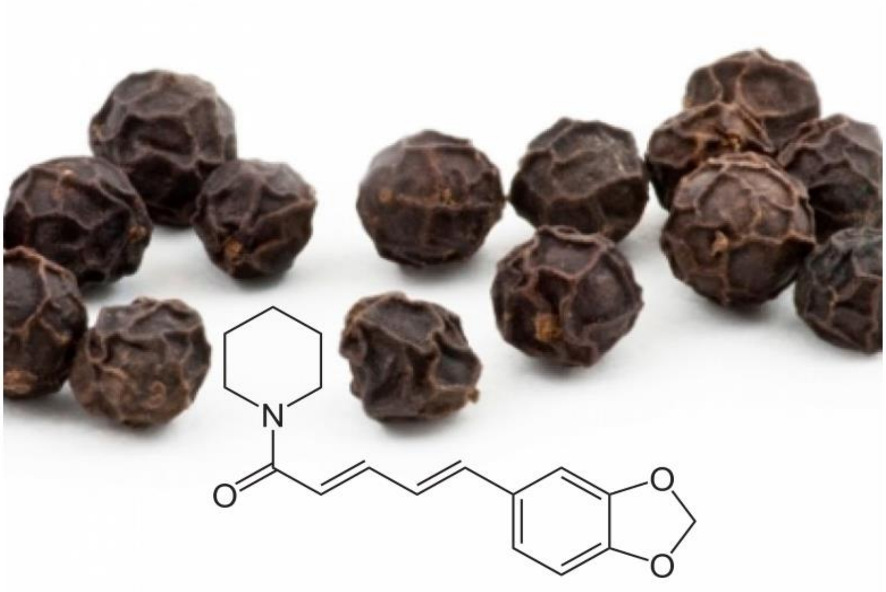


Figure 7: Piperine issued from black pepper

Near piperine, the volatile (essential) oil for odor and flavor as well as for massage [79] contribute to its value. Black pepper contains also (11–14%) protein, (47–53%) fiber, and (10–13.5%) starch [80].

The content of piperine, volatile oil, starch, and fiber can vary markedly in different pepper varieties and is indicative of the quality of black pepper [81]. Black pepper contains about 5–9% of the alkaloids piperine and piperettine and about 1.2– 5% of volatile oil [82]. Essential oil is a small portion of a plant material, which consists mainly of terpenes, sequiterpenes, and their derivatives that are responsible for the characteristic aroma, and imparts the identifying flavor and odor most closely associated with the plant itself [83]. Phytochemical studies as well as progresses in extraction methods and techniques have shown that plants in genus Piper contain a variety of chemical constituents, such as piperolides, propenylphenols, amides, neolignans, lignans, flavonoids, terpenes, and steroids [84,85], that demonstrate cytotoxic, anti-inflammatory, antimycobacterial, insecticidal, antiprotozoal, analgesic, anxiolytic, and antidepressant activities11. Black pepper (Piper *nigrum* L.), which is well known regarded as the king of spices, is also widely used in the traditional medicine in many countries. Piperine is the main chemical constituent of this plant, which has diverse activities, such as central nervous system depression, cytotoxic, anti-inflammatory, and hepatoprotective effects, as well as the ability to enhance bioavailability.

Nakatani *et al.*, in 1986, identified five phenolic amides from *Piper nigrum*, seven compounds from *P. retrofractum*, and two compounds from *P. baccatum*. All the phenolic amides possess significant antioxidant activities that are more effective than the naturally occurring antioxidant, alpha-tocopherol. One amide, feruperine, has antioxidant activity as high as the synthetic antioxidants, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) [86].

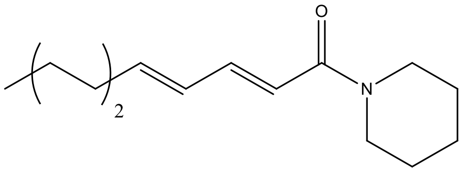
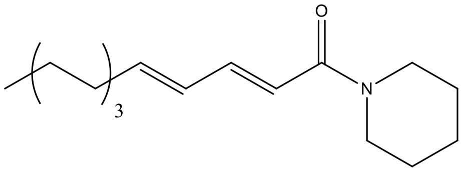
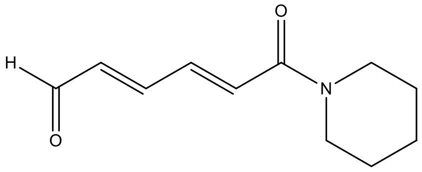
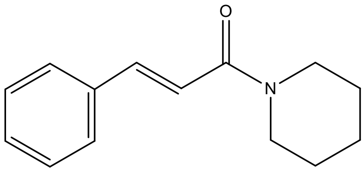
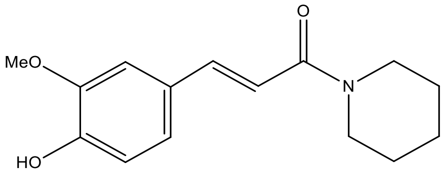
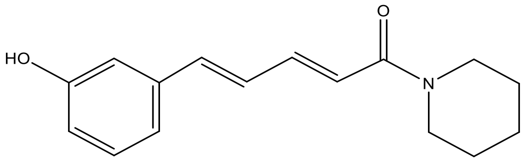
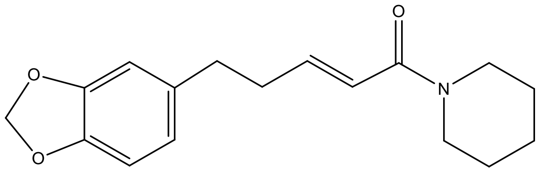
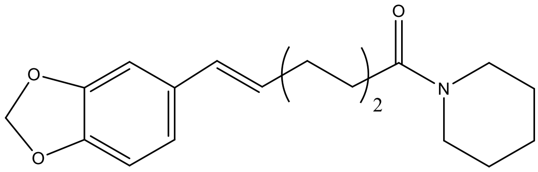
Black pepper contains 47%-53% fiber, 11%-14% protein, and 10%-13.5% starch [87,88]. It is also a source of potassium, calcium, manganese, iron, and minute amounts of vitamins K and C. Essential oil is present in a small portion of pepper plant material, which consists of terpenes, sesquiterpenes, and their derivatives, which are the reason for the aroma and flavor of pepper plant [87,88]. Essential oils of black pepper are extracted from seeds and leaves. More than 250 volatiles have been reported to be present in this valuable spice. The main compounds detected are germacrene D, limonene, b-pinene, a-phellandrene, b-caryophyllene, a-pinene, and cis-b-ocimene.

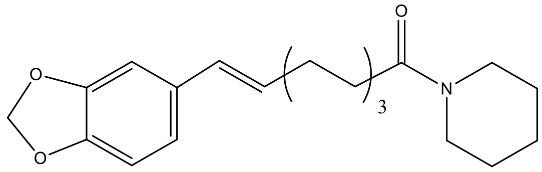
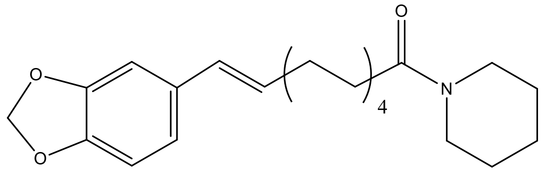
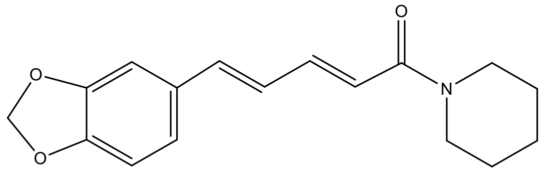
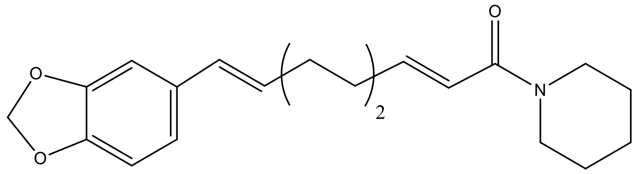
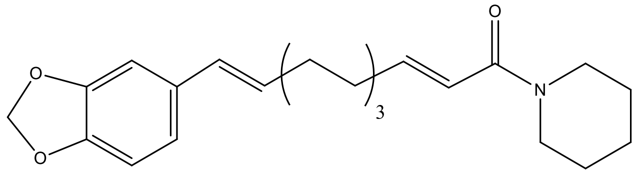
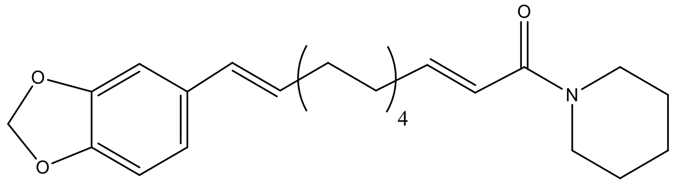
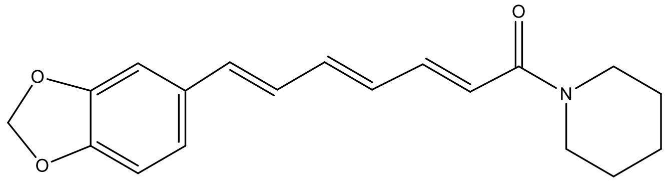
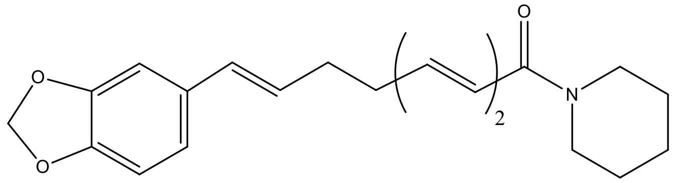
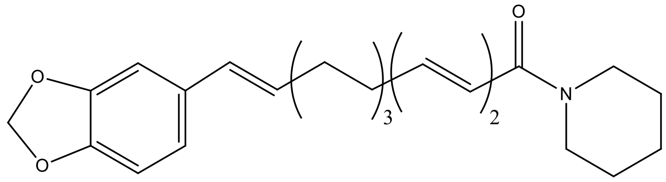
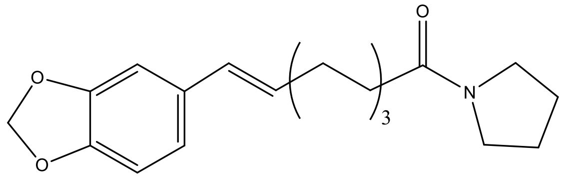
Ravindran and Peter, [89,90], demonstrated that piperine exists as 4 isomeric structures: piperine (trans-trans isomer), isopiperine (cis-trans isomer), chavicine (cis-cis isomer), and isochavicine (trans-cis isomer); however, the 3 geometric isomers of piperine have almost no pungency [68]. Later investigations have demonstrated the presence of other alkaloids, including piperanine, piperettine, piperylin A, piperolein B, and pipericine, all possessing some degree of pungency in the pepper extract. Nevertheless, the overall contribution of these alkaloids to pungency of pepper was found to be small.

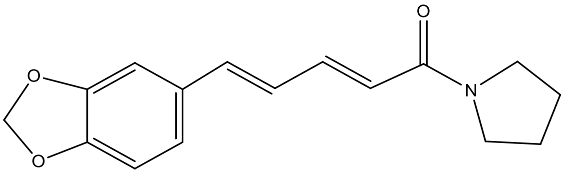
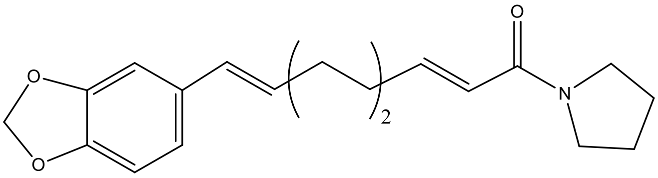
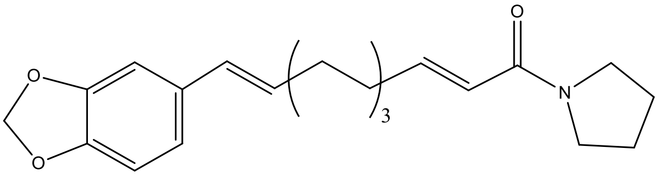
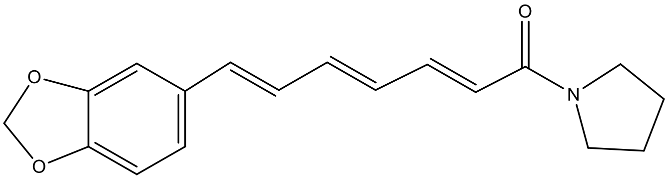
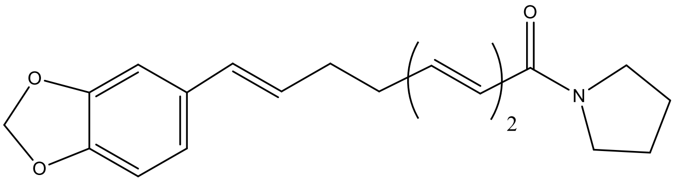
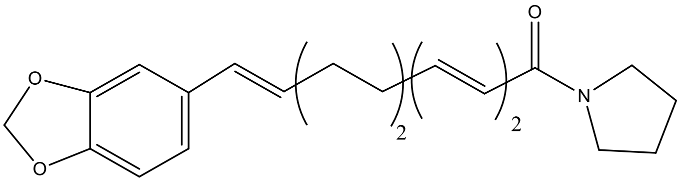
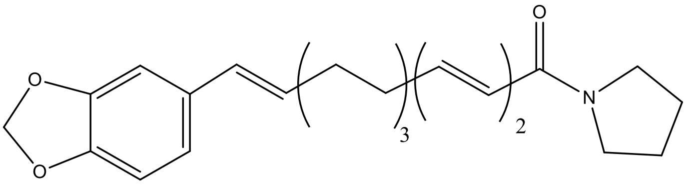
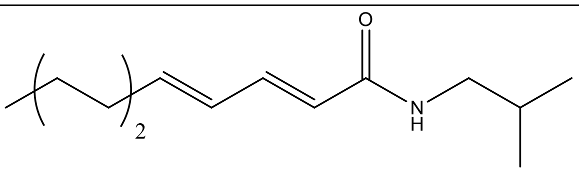
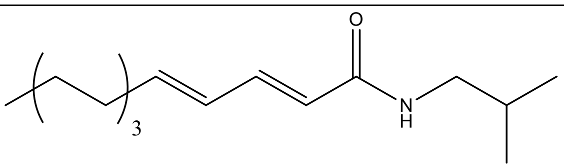
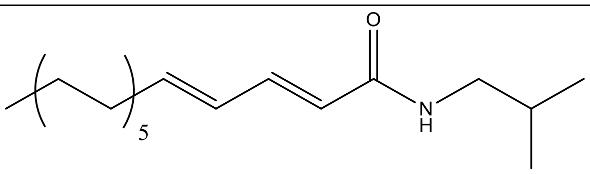
4.1. Major compounds

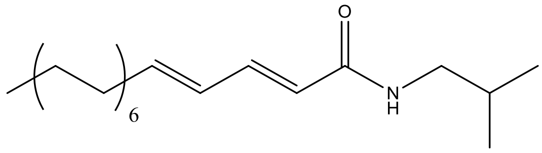
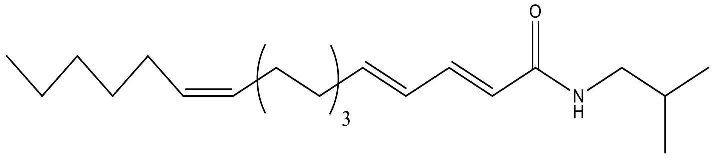
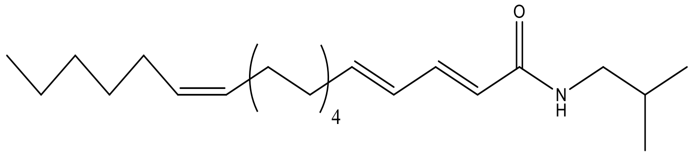
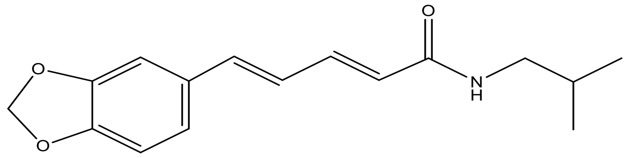
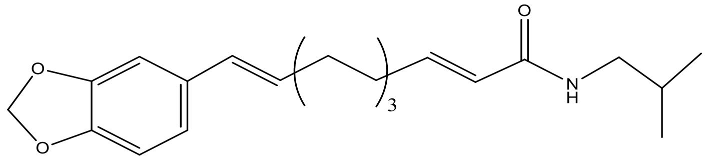
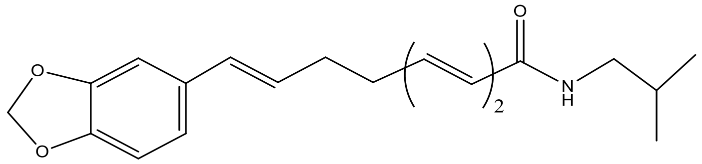
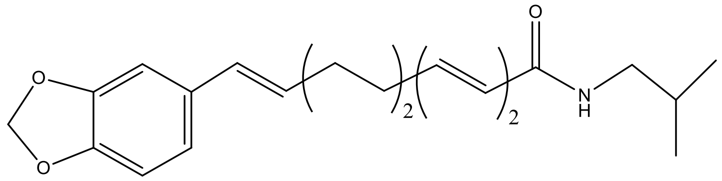
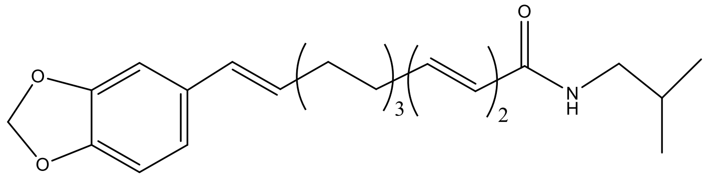
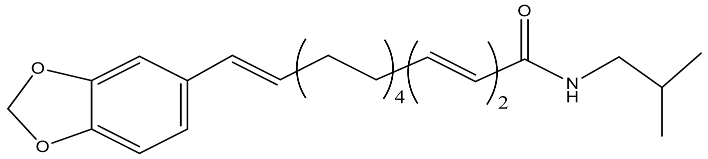
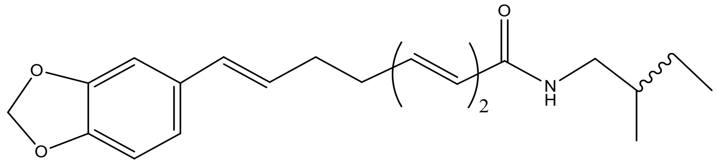
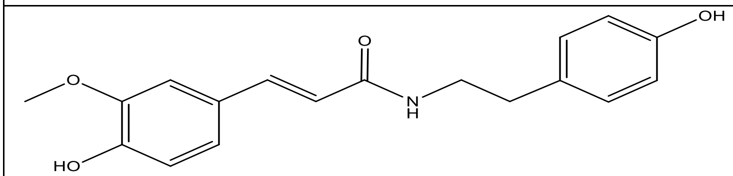
The major components of black pepper “piperine” and nearest ones are classified as bioactive molecules as shown later [91]. Structures of compounds 1−55 isolated from *Piper nigrum* found in the literature (Table 1):

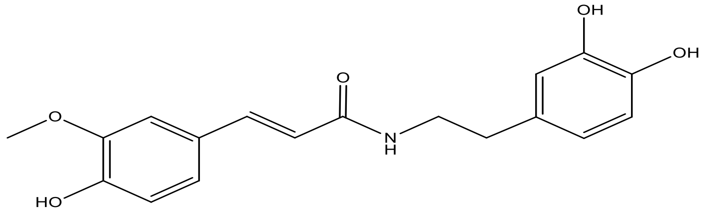
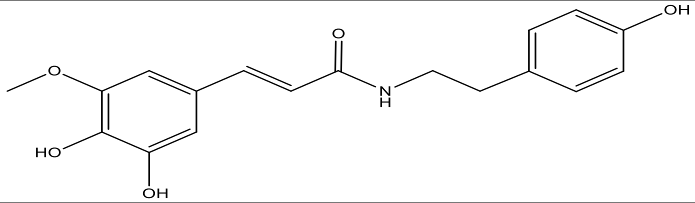
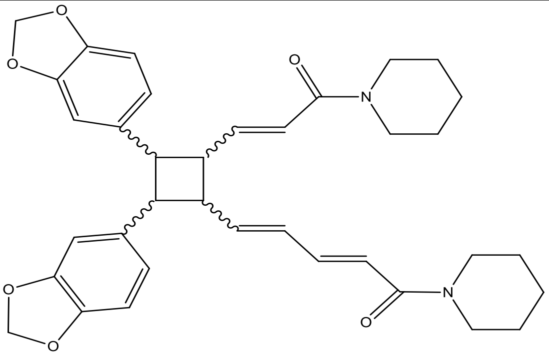
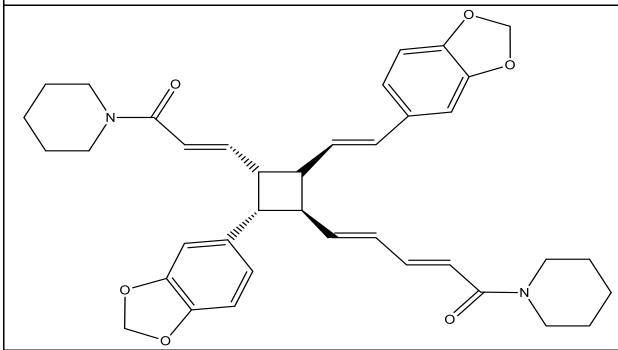
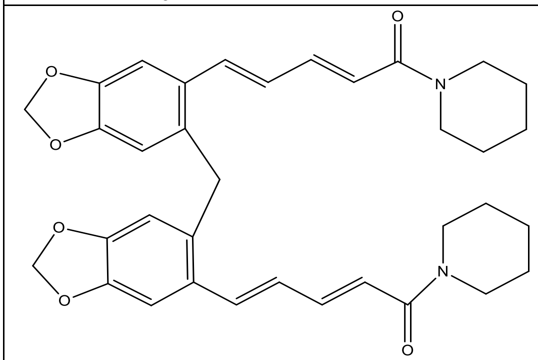
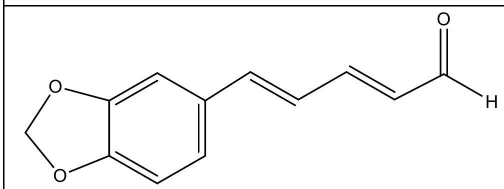
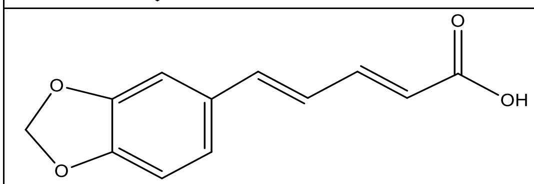
Table 1: Structures of compounds **1**−**55** isolated from *Piper nigrum*.

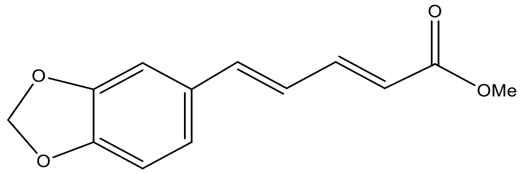
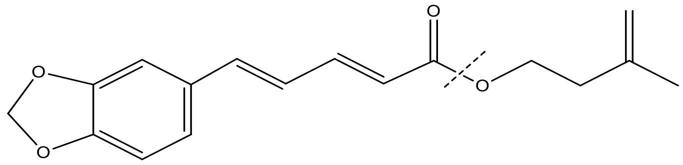
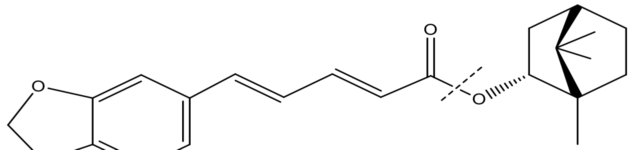
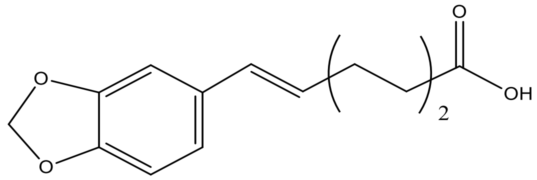
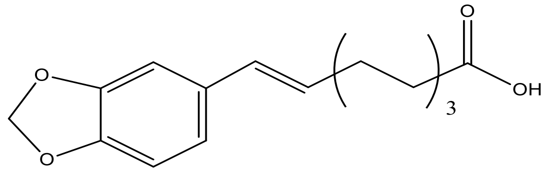
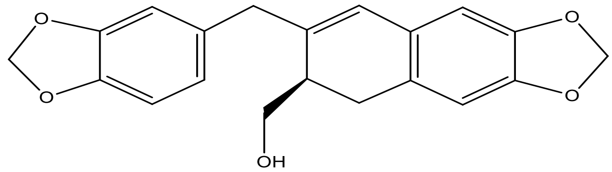
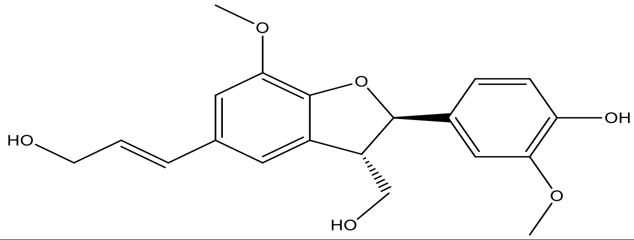
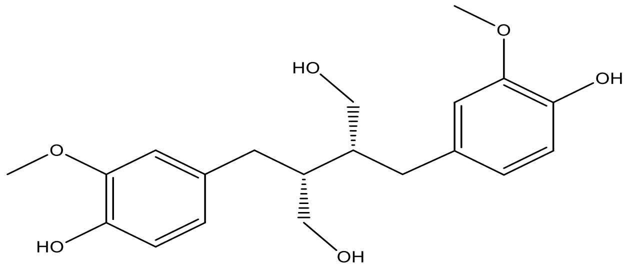
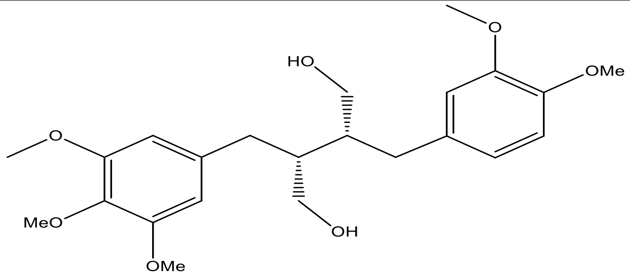
Structure	Name	Ref
	Achilleamide (1)	[92]
	2,4-(E,E)-dodecadienyl piperidide (2)	[93]
	Pipernigramide A (3)	[94]
	1-cinnamoylpiperidine (4)	[95]
	N-trans-feruloyl piperidine (5)	[96]
	Coumaperine (6)	[97]
	Piperanine (7)	[98]
	Piperoleine A (8)	[99]

	Piperoleine B (9)	[100]
	Pipernigramide B (10)	[94]
	Piperine (11)	[100]
	Pipernonaline (12)	[101]
	piperchabamide B (13)	[102]
	Piperchabamide C (14)	[99]
	Piperettine (15)	[100]
	Dehydropipernonaline (16)	[101]
	(2E,4E,12E)-13-(3,4-methylenedioxyphenyl)-1-(1-piperidinyl)-2,4,12-tridecatrien-1-one (17)	[103]
	Tricholeine (18)	[99]

	Piperyline (19)	[100]
	Brachyamide B (20)	[102]
	1-[(2E,10E)-11-(3,4-methylenedioxyphenyl)-2,10-undecenoyl]pyrrolidine (21)	[13]
	Piperettyline (22)	[99]
	6,7-dehydrobrachyamide B (23)	[99]
	1-[(2E,4E,10E)-11-(3,4-methylenedioxyphenyl)-2,4,10-undecatrienoyl] pyrrolidine (24)	[105]
	Brachyamide A (25)	[100]
	Pellitorine (26)	[101]
	Kalecide (27)	[99]
	N-isobutyl-(2E,4E)-hexadecadienamide (28)	[102]

	N-isobutyl-(2E,4E)-octadecadienamide (29)	[102]
	N-isobutyl-(2E,4E,12Z)-octadeca-2,4,12-trienamide (30)	[100]
	N-isobutyl-(2E,4E,14Z)-eicosa-2,4,14-trienamide (31)	[100]
	Piperlonguminine (32)	[100]
	Piperchabamide D (33)	[101]
	Retrofractamide A (34)	[100]
	Retrofractamide B (35)	[102]
	Guineensine (36)	[10]
	Brachystamide B (37)	[99]
	Pipernigramide C (38)	[94]
	Ferulyltyramine (39)	[99]

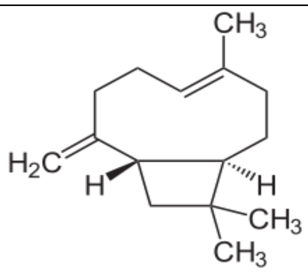
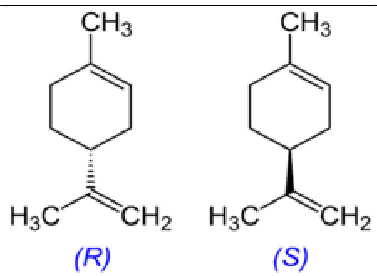
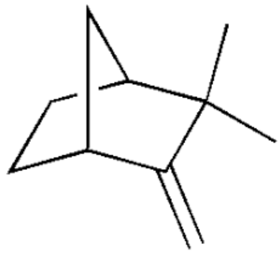
	N-trans-feruloyldopamine (40)	[106]
	Pipernigramide D (41)	[94]
	Pipernigramide E (42)	[94]
	Pipernigramide F (43)	[94]
	Pipernigramide G (44)	[94]
	(2E,4E)-5-(3,4-methylenedioxyphenyl)-2,4-Pentadienal (45)	[107]
	Piperic acid (46)	[108]

	Methyl piperate (47)	[108]
	Pipernigrester A (48)	[94]
	(+)-Bornyl piperate (49)	[109]
	(6E)-7-(3,4-Methylenedioxyphenyl)-heptenoic acid (50)	[104]
	(8E)-9-(3,4-Methylenedioxyphenyl)-nonenoic acid (51)	[104]
	Cubebinol (52)	[110]
	(-)-Dehydrodiconiferyl alcohol (53)	[111]
	(-)-Secoisolariciresinol (54)	[112]
	2R,3R)-2-[(3,4-Dimethoxyphenyl)methyl]-3-[(3,4,5-trimethoxyphenyl)methyl]-1,4-butanediol (55)	[113]

4.2. Essential oil of Black Pepper

Although some studies have been carried out to determine the ingredients of black pepper Essential Oil (EO) cultivated in various regions of the world, but there is little data about some physicochemical characteristics of EO of black pepper cultivated in Chittagong, Bangladesh. The major components of black pepper EO were caryophyllene (19.12%), limonene (9.74%), and camphene (8.44%) (Table 2). The contents of moisture, dry matter, protein, fatty oil, ash, carbohydrate, and crude fiber in black pepper samples were determined as 2.20, 96.12, 12.66, 14.41, 12.49, 42.56, and 5.55%, respectively [114].

Table 2: some components of essential oil of BP [114]

 Caryophyllene (sesquiterpene, bicyclic) (19.12%)	 (R) and (S) Limonene (Monoterpene) (9.74%)	 Camphene (monoterpene, bicyclic) (8.44%)

The chemical composition of essential oils obtained by three techniques: classical hydrodistillation (CHD) and by microwave hydrodistillation on low and high microwave power was given in Table 3. Results showed that in the CHD extraction oil, β-caryophyllene as sesquiterpene hydrocarbon was the major compound present with 49.80%. MWHP extraction oil realized at a high microwave power (700W) was also rich in β-caryophyllene with relatively the same amount 52.67%.

Table 3: some components of essential oil of BP [115]

Relative amount (%)				
	Microwave extraction (%)	MWLP	MWHP	Classical extraction (CHD)
Compounds	**RT[(a)]**	**280w**	**700w**	
Sabinene	9.11	-	3.01	
α-Copaene	22.92	5.95	8.86	5.76
Germancene-D	23.39	1.13	1.83	1.68
Caryophyllene	24.32	8.25	52.67	49.80
α-Humulene	25.30	0.72	4.00	3.86
Cubenol	27.20	3.85	5.10	5.20
Caryophyllene oxide	29.08	63.13	4.79	2.46

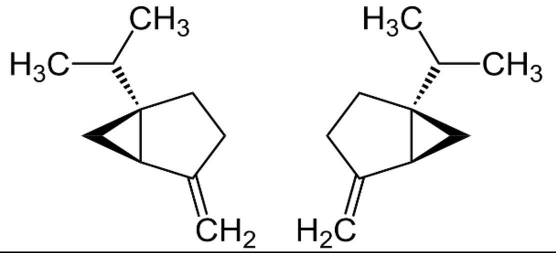
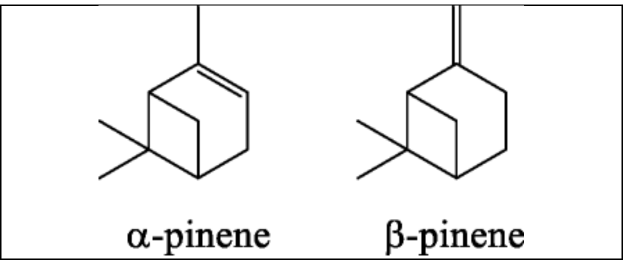
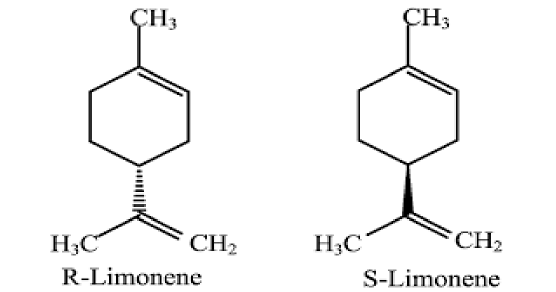
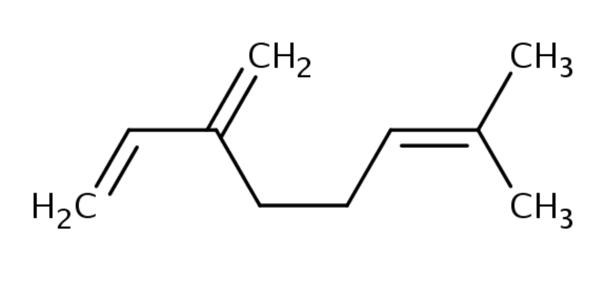
(a) Retention time in GC analysis
(b) Microwave power used in microwave hydrodistllation of essential oils

However, at low power 280W, the oxygenated compound caryophyllene oxide was selectively extracted with a high amount 63.13% because of his strongly microwave absorption [16]. In the case, β-caryophyllene as non-polar compound presented a lower percentage 8.25% [115]. In comparison of the essential oil of Piper majusculum from Piperaceae family was obtained by hydrodistillation technique, twelve components accounting were identified for 93.79% of the total oil. The major components were β-caryophyllene (17.27%), caryophyllene oxide (14.26%), α-selinene (14.21%) and cis-calamenene (9.62%) [116].

4.3. Aroma Substances

In some spice plants, the odour corresponds with that of the main components of the volatile fraction. Aroma compounds produced by plants, mainly attract pollinators as bees, seed dispersers and provide defence against pests or pathogens. However, in humans, about 300 active olfactory receptor genes are involved to detect thousands of different aroma compounds and modulates expression of different metabolic genes regulating human psychophysiological activity, brain function, pharmacological signalling, and therapeutic potential [117]. Belitz et al. [118] in their book "Food Chemistry" summarized the important odorants of black pepper usually in lower concentrations. The aroma of ground pepper is not stable due to losses of important aroma substances with time. The most known aroma are (−)-Sabinene, (+)-Sabinene, (−)-α-Pinene, (−)-β-Pinene, (S)-Limonene, (+)-β-Pinene, (R)-Limonene, Myrcene … (Table 4).

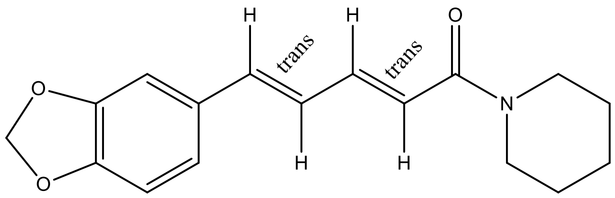
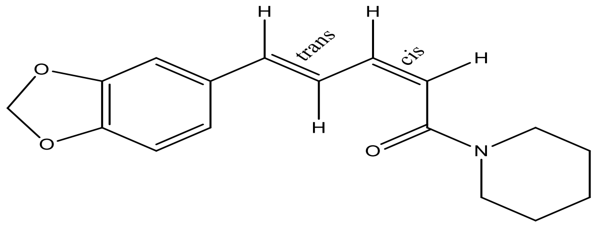
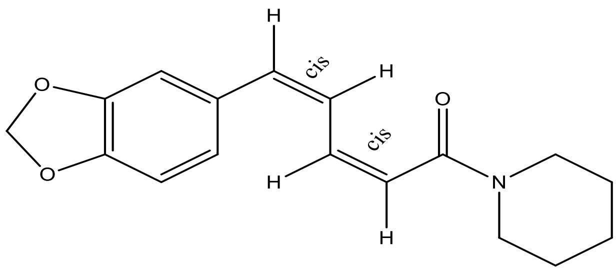
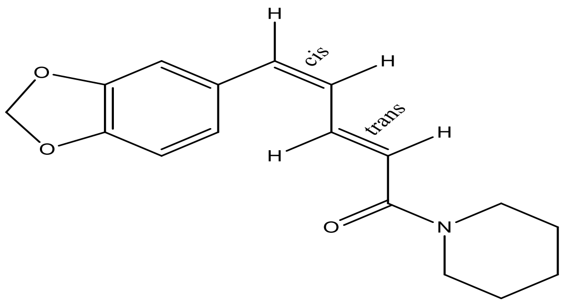
Table 4: Major aroma components of essential oil of BP [118]

	
Sabinene	Pinene
	
Limonene	Myrcene

4.4. Substances with Pungent Taste

The hot burning pungent taste of black pepper is caused by the non-volatile compounds: piperine as the most important pungent substance, piperanine and Piperylin as shown above in Table 1. Pepper is sensitive to light since the trans,trans-diene system of piperine isomerizes to the cis,trans-diene system of the almost tasteless isochavicin on exposure to light [119]. As shown in Table 5.

Table 5: piperine molecule at four isomeres

 **piperine = E,E-(trans-trans)-piperine**	 **isopiperine = Z,E-(cis-trans)-piperine**
 **Chavicine = Z,Z-(cis-cis)-piperine**	 **Isochavicine = E,Z-(tans-cis)-piperine**

Srinvisan [41] concluded that piperine has been experimentally demonstrated by a number of independent investigators to possess diverse physiological effects. It has been evidenced to protect against oxidative damage by inhibiting or quenching free radicals and lower lipid peroxidation and beneficially influence cellular thiols, antioxidant molecules and antioxidant enzymes in different situations of oxidative stress. The most far-reaching attribute of piperine has been its inhibitory influence on hepatic, pulmonary, and intestinal drug metabolizing system. It strongly inhibits a particular cytochrome. Both black pepper and piperine have been evidenced to have a definite effect on intestinal motility, the antidiarrhoral property, and on the ultrastructure of intestinal microvilli improving the absorbability of nutrients. Among other physiological effects piperine exerts, its potential antifertililty influence on the reproductive system has been clearly established in in vitro and animal systems.

5. Medical uses of Black Pepper

Its distinctive pungent flavor due to the presence of an alkaloid piperine, make black pepper the most utilised both in cooking and medicinal treatments. Databases are very rich offer infinite documents on the use of piperine in traditional therapies of Chinese as well as in Indian medicine. The chemical structural of piperine containing three parts : aliphatic chain headed by both amide and aromatic moieties offers this wide applications (Figure 8).

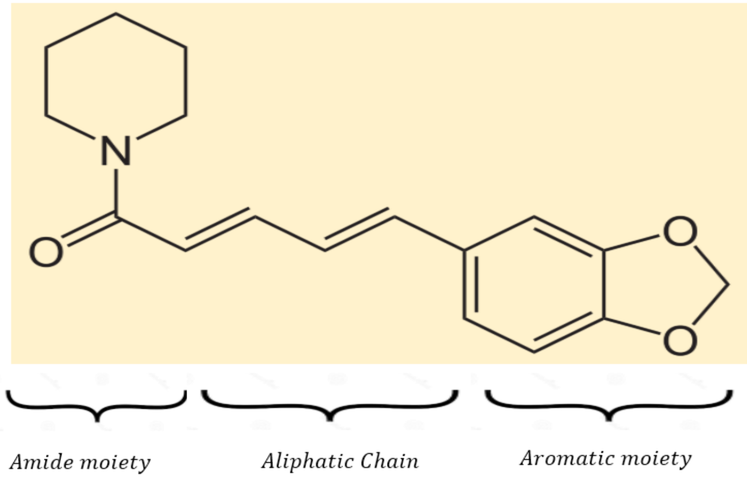


Figure 8: Synergistic oft he three parts of piperine molecule

Survey of literature show the various biological activities such as anti-infective, antimicrobial, insecticidal, anti-inflammatory, antiamoebic, antiulcer, and antidepressant of piperine [120-129]. Piperine can be also used widely in pain management, chills, rheumatism arthritis, influenza, and fever as well as hypotension, vascular cell modulation, and anti-cancer activity. It also acts on many enzyme systems (including *p*-glycoproteins) [130-136]. Piperine has been shown to help digestion of food i.e. stimulation of appetite, the enhancement of blood circulation, salivation, to have antioxidant activity, and to enhance drug bioavailability [137-139].

Piperine, a pungent alkaloid found in pepper, helps increase the absorption of selenium, B-group vitamins, and beta-carotene, among other nutrients. It also helps stimulate saliva secretion, which increases the production of digestive juices, responsible for breaking down proteins, increasing digestibility and reducing the possibility of heartburn and other gastrointestinal issues. Piperine also increases the bioavailability of certain compounds. This is especially true when it comes to curcumin, the active compound of turmeric that helps fight inflammation. In a study published in Planta Medica (1998), it was found that piperine enhanced the extent of absorption (bioavailability) and serum concentration of curcumin in both rats and humans with no unfavorable side effects. Piperine also interferes with inflammatory signaling mechanisms and inhibits pro-inflammatory cytokines, which are small proteins secreted by some cells and linked with a number of degenerative diseases. Moreover, black pepper's antioxidant content helps the body to fight and repair the free radicals' damage that contribute to cardiovascular diseases, inflammation, and more [140].

5.1. Antioxidant active chemicals

Black pepper contains an important source of natural antioxidant. The main role of antoxidant protect cells against free radicals, which may play a role in heart disease, cancer and other diseases. Free radicals are molecules produced when your body breaks down food or when you're exposed to tobacco smoke or radiation [141]. The importance of antioxidants for maintaining the physiological functions of liver, kidney, digestive system, and prevention of cardiovascular diseases and cancer has also been highlighted [142]. They have beneficial influence on lipid metabolism efficacy as anti-diabetics. They have ability to stimulate digestion and; have antioxidant; Meghwal and Goswami collected the Antioxidant active chemicals isolated from black pepper : Ascorbic-acid, β-carotene, Camphene, Carvacrol, Eugenol, γ-terpinene, Lauric-acid, Linalyl-acetate, methyl-eugenol, myrcene, myristic-acid, myristicin, palmitic-acid, piperine, terpinen-4-ol, ubiquinone [136].

Significant correlation between EPR and thiobarbituric acid methods was assessed by study of antioxidant activity changes in relation to irradiation doses and also in the case of spice storage, between EPR and reducing power methods [143]. Peppercorns especially black pepper, which constitutes an important component in the diet of many sub-Saharan and oriental countries, can therefore be promoted for their nutritional importance as antioxidants and radical scavengers [144].

The physico-chemical properties and bio-efficacies, antioxidant activities, of the encapsulated black pepper essential oil in hydroxypropyl-β-cyclodextrin (HPβCD), in comparison with the major ingredient in the oil, β-caryophyllene was improved by 4 times [145]. The biological control of root-knot nematode (*Meloidogyne incognita*) by aqueous leaf extracts of black pepper was investigated and could be a possible replacement for synthetic nematicides with fewer side effects in the soil and on crops [146]. Nanoliposomes of piperine-rich extract of black pepper holds promise as nutraceuticals in designer food applications [147]. Also, Vidangadi churna is a traditional polyherbal ayurvedic formulation used in conditions like antifertility, antibacterial, antiprotozoal properties, abdominal disorders, lung diseases and antiinflamatory. It's composed of Embelia ribes (false black pepper fruit), Hordeum vulgare, Mallotus philippinensis, Terminalia chebula and rock salt. It showed significant antioxidant activity [148]. Black pepper (Piper nigrum L.) which is a very widely used spice, known for its pungent constituent piperine. However, in addition to its culinary uses, pepper has important medicinal and preservative properties, and, more recently, piperine has been shown to have fundamental effects on p-glycoprotein and many enzyme systems, leading to biotransformative effects including chemoprevention, detoxification, and enhancement of the absorption and bioavailability of herbal and conventional drugs. Based on modern cell, animal, and human studies, piperine has been found to have immunomodulatory, anti-oxidant, anti-asthmatic, anti-carcinogenic, anti-inflammatory, anti-ulcer, and antiamoebic properties [149]. Excessive free radical generation overbalancing the rate of their removal leads to oxidative stress. Oxidative stress has been implicated in cardiovascular disease, inflammatory diseases, cancer, and other chronic diseases. The antioxidative effects of turmeric/curcumin, clove/eugenol, red pepper/capsaicin, black pepper/piperine, ginger/gingerol, garlic, onion, and fenugreek, which have been extensively studied and evidenced as potential antioxidants [150].

5.2. Cholesterol Lowering and Immune Enhancer

Black pepper and piperine reduce cholesterol uptake and enhance translocation of cholesterol transporter proteins. It enhances digestion process by helping faster break down of larger fat molecules into easily digestible simple molecules and prevents the accumulation of fat in body. Black pepper exhibits immunomodulatory effect on human body [69,77,151,152].

Black and red pepper has been used for centuries as spice or food with healthful applications and suggest that dietary inclusion of peppers may attenuate some cardiometabolic risk markers associated to Western-style diet [153]. Piperaceae, a Latin name derived from Greek, which in turn originates from the Arabic word babary-black pepper, is considered one of the largest families of basal dicots, found in tropical and subtropical regions of both hemispheres. They are also used in folk medicine for treatment of many diseases in several countries including Brazil, China, India, Jamaica and Mexico. Pharmacol. studies of Piper species point toward the vast potential of these plants to treat various diseases. Many of these species are biol. active and have shown antitumor, antimicrobial, antioxidant, insecticidal, anti-inflammatory, antinociceptive, enzyme inhibitor, antiparasitic, antiplatelet, piscicide, allelopathic, antiophidic, anxiolytic, antidepressant, antidiabetic, hepatoprotective, amebicide and diuretic possibilities [154]. Comprehensive assessment effectiveness and food products quality forecast was substantiated using organoleptic profiles construction and usage of differential equations. The pastas with spices based on soft diet cottage cheese produced of variable recipes quality was selected as an object of the study. In the pastas compounds such spices as allspice, black pepper, ginger, cinnamon, anise, cloves, cardamom, fenugreek and nutmeg were used in amt. of 0.27...1.1%. The analytical research results on product quality were obtained from organoleptic parameters and content of biological active substances (tannin, catechin, and rutin) with usage of symbolic computer mathematics and graphic images methods [155]. Diabetes mellitus is a metabolic disorder and emerging pandemic of the 21st century. Piperine, the chief alkaloid present in Piper nigrum (black pepper), has a wide array of uses in alternative and complementary therapies. The effect of piperine on blood glucose level was studied in streptozotocin induced diabetic rats in subacute study models. The results suggest that piperine (50mg/kg) showed antidiabetic activity in streptozotocin induced diabetic rats [156]. Black pepper oil and its major components were investigated for the biological activities related to the prevention of Alzheimer's Disease via AChE inhibition and anti-inflammatory activity via COX-2 inhibition [157]. An improved method of sample preparation was used in a microplate assay to evaluate the bactericidal activity levels of 96 essential oils including Black pepper oil against Campylobacter jejuni, Escherichia coli, there are possible significance of these results with regard to food microbiological is discussed [158].

5.3. Anticancer

The cancer is the disease of today or of the century and cancer research is the subject of trillions of papers and research into new drugs has become an economic issue bringing in trillions of dollars. Natural products have been used for the treatment of various diseases and are becoming an important research area for drug discovery [159]. Amaral et al resumed that Since the 1980s, a total of 174 new compounds with indications for cancer treatment have been approved for commercialization, of which a total of 93 (53%) were natural products or derived directly or based on them. Due to the relative ease of access to the plants, most of the discoveries of anticancer compounds were derived from plants, among these discoveries the drug obtained from the bark of Taxus brevifolia (paclitaxel) presents one of the most successful stories in plant-based research [160]. Piperine exerts antitumor activities in a variety of cancers [132,161-164]. Literature pointed on the characteristic pungency and biting taste of pepper is due high content of piperine in it. Piperine has been exploited for many therapeutic purposes in the past and is anticipated to remain so in the future. Piperine is an important dietary phytochemical due to its presence in spicy foods as well as its pharamacological activities (antiinflammatory, antimetastatic, anti-cancer, larvicidal, leishmanicidal, immunosuppressive, antimycobacterial, and antiparasitic activities) [132,165-172].

Different studies have shown that the regular consumption of certain vegetables and fruits can reduce disease risks. Piperine, which give chilli peppers and black pepper and its analogues have a favourable toxicity profile, but are cytotoxic towards a range of cancer cell lines including blood cancer and lung cancer [173]. Both PI3K/AKT/mTOR/S6K1 and mitogen activated protein kinase (MAPK) signaling cascades play an important role in cell proliferation, survival, angiogenesis, and metastasis of tumor cells. The black pepper (Piper nigrum L.) is very active against human prostate and breast cancer cells. these findings suggest that CPO can interfere with multiple signaling cascades involved in tumorigenesis and used as a potential therapeutic candidate for both the prevention and treatment of cancer [174].

6. Biotechnology of Black Pepper

6. 1. Black pepper production and protection

Black pepper is one of the worldwide most used spices. It's is obtained from unripe fruits, called peppercorns, of the plant species *Piper nigrum* L, of the *Piperaceae* family. The productivity of black pepper (*Pipper nigrum*) in mainly linked to (1) genetic potential of the plant, (2) biotic and abiotic stress factors, and (3) level of adoption of good agricultural practices [175]. The lack of control of these factors can compromise the productivity and/or the quality of the final product. Some standards to be implemented in crop production (vegetative production, irrigation, nutrients, etc…) and crop protection from insects and diseases are reported by [175-177]. The major diseases affecting pepper plantations are caused by nematodes and fungus (*Phytophthora capsici*) on foot, while leaf spots are caused by fungus (*Colletotrichum gloeosporioides*) and bacteria (*Xanthomonas campestris pv. beticola*) diseases [175,176]. Biotechnology approaches are considered as promising tools to control of pathogens via development of plant resistance and biopesticides [176]. Among bacteria, strains of *Pseudomonas fluorescens*, *Bacillus pumilis, B. macerans* and *B. circulans* demonstrated efficiency in nematode control when used as biocontrol agent, and strains of *Trichoderma* sp showed their protective effect against nematodes and *Phytophthora capsici* [178]. Among some black pepper cultivars, one hybrid and two wild germplasms, showed promising result in resistance to *Phytophthora capsici* [179].

6. 2. Black pepper processing

The black pepper processing includes the post-harvest operations of the fruits. The main unit operations, mostly practiced, are reported in Figure 9. Black pepper is obtained from dried immature berries, harvested when one or more berries turn to orange or red color on a spike [175]. During maturation of fruits, the piperine and starch contents increase, while the volatile oils and non-volatile resins decrease [180]. Therefore, the fruits should be harvested at the same and carefully chosen stage of maturity, to ensure a low crop loss during processing and a uniform final product with high quality. The spikes were then subject of threshing operation, which consists of harvesting berries from spikes, mostly done by hand or using mechanical machine. The fruits are then washed in running tap water, then blanched in boiling water, for one to five minutes, and then let to sun drying for 2 to 5 days [181].

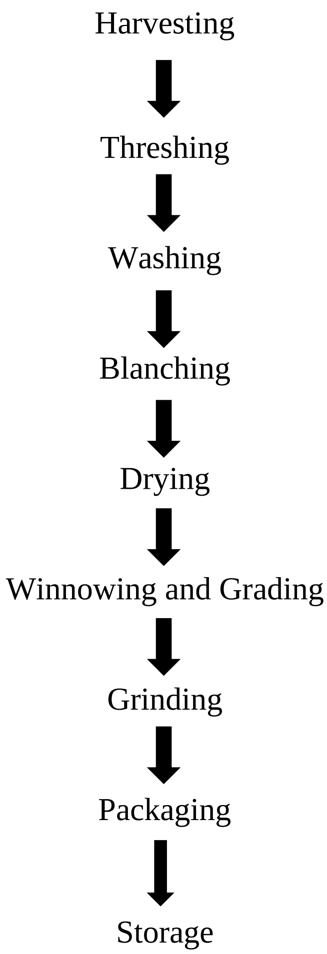


Figure 9. Flow diagram of black pepper processing [182].

Blanching allows the oxidation of phenols by phenolase enzymes, leading to the development of a brown color in fruits [183,184], and permits also the decontamination of fruits by reducing their microbial load. However, the blanching period should be lower as far as possible to avoid enzyme denaturation and loss of volatile flavor compounds. The dried fruits are then subject of winnowing to remove extraneous materials (vegetable seeds, leaves, sand, dust, small stones and light foreign matter, etc.). The dried and destoned pepper fruits are then graded, then grinded and packed.

6. 3. Quality control of black pepper

During processing, black pepper is subject to various physical, chemical and microbiological defects. High concentrations of toxic elements [185] and pathogenic microorganisms [186] were detected in processed peppers. The quality control of the product along the processing chain is mandatory to avoid risks associated with these defects (FAO/WHO, 1995) [187]. The effectiveness of some treatments in pathogens and spoilage microorganisms' decontamination of black pepper was demonstrated, such as sterilization and microwave treatments [188] and gaseous acetic acid treatment [189]. In addition, the standards adopted by FAO/WHO (CXS-326-2017) [190] for black pepper commercialization, include color, odor and flavor characteristics, as well as physical (size, shape, extraneous matter, etc.) and chemical (moisture, piperine, volatile oil, non-volatile ether extract, ash, etc.) properties (FAO/WHO, 2017). The sun drying between polythene sheets for 2-3 hours, followed by direct sun drying for 3-4 days produced dried berries with good color, higher aroma, better oleoresin and piperine contents and high market price [190].

The quality of black pepper is related mainly to the piperine, which is the most abundant alkaloid responsible of pungent taste of black peppers [191]. The content of piperine in black pepper is of 2% to 9% of the product, depending on the growing conditions [192, 193], and maturity stage of fruits [166].

7. Pepper : diseases and Managements

Despite its very diverse chemical composition, pepper is attacked by pests and diseases and consequently influence its production. Biotic agents of disease of pepper include fungi, bacteria, nematodes, and viruses. Abiotic disorders include a number of unfavorable cultural or climatic conditions, such as sunlight, nutrient deficiency, and temperature excesses [194-199]. Diseases affect all parts of the pepper plant including the foliage, stems, roots, fruit, and young seedlings. Fungi and bacteria cause a variety of symptoms such as leaf and fruit spotting, wilting and plant death. Typical symptoms of viral infections are stunting, mottling of foliage and fruit, and small, misshapen fruit. Abiotic disorders such as sunscalding or blossom end rot greatly interfere with the fruit quality and reduces yield [200-203]. Management of diseases begins prior to planting of the crop and many techniques are used to minimize losses due to disease problems [204]. Control methods include, but are not limited to, the use of cultivars with resistance to diseases, pathogen-free seeds, sterilized equipment for transplant production, rouging and eradication of diseased plants and alternative hosts, field sites that are pathogen-free and isolated from other solanaceous crops, soil fumigation, and application of pesticides and other disease-suppression compounds [205]. It was also confirmed that residues of imidacloprid and abamactine remain in vegetables: tomatoes, cucumbers and peppers, especially after a few days of spraying of pesticides and the amounts of imidacloprid and abamactine residues were very high after the first day of spraying. Until the fifth day of spraying, the amounts of residues of the two pesticides remained high (due to high concentrations used by farmers) and this may pose a serious risk to human health via food consumption. However, photodegradation caused a decrease of the pesticide residues in the plant parts [206].

8. Other applications

8.1. Anticorrosion

Their wide uses in different medical fields incited researchers to test extract, oil and isolated compounds of black pepper as Corrosion inhibitor of metallic materials in aggressive media [114, 207-215]. The molecular structures of various components of black pepper having aromatic rings, double bonds as well as heteroatoms facilitating their reactivity at the metal surface by adsorption to form coordination with metallic atoms. Black pepper created a barrier film at the metal surface leading to its protection against corrosion process. Effect of black pepper (BP) extract and its piperine, piperanine and piperic acid isolated from BP on corrosion of C38 steel in 1 M HCl solution was investigated by weight loss method. Piperine and piperanine were isolated by ethanol in yield 6 from ground BP [215]. Results obtained from weight loss measurements indicate that the natural compounds tested exhibit higher efficiency exceeding 95% at 2g/L. The presence of piperine decreases hugely the corrosion rate and its inhibition efficiency (E%) increases with concentration to attain 99 % at 10^{-3}M. Piperine adsorbs on the steel surface according Langmuir isotherm. Adsorption enthalpy were determined and discussed. Effect of temperature was also investigated and activation parameters were evaluated (Table 6) [212-214]. The lower values of free enthalpy, ΔG^{o}_{ads} < -40 kJ/mol, indicated that piperine and piperanine acted via chemisorption on the iron surface. Also, the activation energy (E_a) revealed that corrosion process is blocked in the presence of piperine and piperanine accompanied by an increase of E_a.

Table 6. Corrosion data of steel in 1M HCl without and with 2g/L BP extract or 10-3 mol L-1 of piperine, in the temperature range 40–70 °C at 1 h [211].

	Temperature °(C)	W_{corr}(mg.cm2.h-1)	Ew (%)
1M HCl	40	2.604	-
	50	4.834	-
	60	9.781	-
	70	13.235	-
Black Pepper extract	40	0.143	94.5
	50	0.277	94.2
	60	0.536	93.1
	70	3.257	75.3
Piperine	40	0.150	94.2
	50	0.280	94.1
	60	0.480	93.7
	70	3.890	70.6

8.2. Organotin (IV) derivative of Piperic acid

Two organotin (IV) derivatives have been prepared from piperic acid, the former is obtained by hydrolysis of piperine, which is extracted from black pepper. The two complexes {[n-Bu_2SnO_2C-$(CH=CH)_2$-$C_7H_5O_2]_2O\}_2$ 1, and [Ph_3SnO_2C-$(CH=CH)_2$-$C_7H_5O_2$]n 2, have been characterized by IR, 1H and 13 C NMR spectroscopic techniques. Single crystal diffraction studies were made to determine the structures of the two compounds 1 and 2. Compound 1 crystallizes in the triclinic system (P\-1) and Compound 2 crystallizes in the monoclinic system (P21/c) (Figure 10) [213].

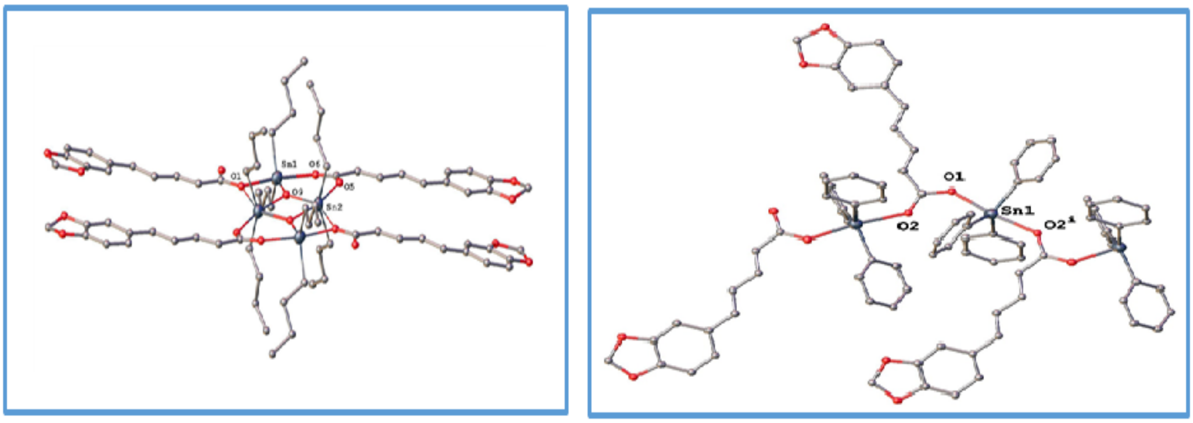


Figure 10: organotin (IV) carboxylates of natural origin pepiric acid (black pepper) [213].

The title compounds were evaluated for their biological activities against a range of cancer cell lines (BT-474, MDA-MB-231, AU565), Chronic myeloid leukemia cell line (K562), Lung cancer cell line (H460) and normal cell line 3T3 mouse fibroblast (Table 7).

Table 7: IC_{50} Value of compounds **1** and **2** against BT-474, H-460, K562, MDA-MB-231 et AU565 [215].

Cytotoxicity and anti-cancer assay : IC_{50} [μM], NA : Not Active						
Comp	BT-474	H-460	K562	MDA-MB231	AU565	Cytotoxicity assay against 3T3 cell line
(1)	6.50 ± 0.80	0.10 ± 0.03	2.60 ± 0.15	6.50 ± 0.80	3.73 ± 0.65	10,70 ± 0,05
(2)	0.17 ± 0.05	NA	0.14 ± 0.00	0.17 ± 0.05	0.12 ± 0.01	10,10 ±0,005
Standard Drug	Doxorubicine 2.10 ± 0.01	Doxorubicine 0.20 ± 0.03	Imatinib 1.72 ± 0.29	Doxorubicine 0.57 ± 0.07	Doxorubicine 0.08 ± 0.003	Cycloexamide 0,8 ± 0,10

Especially complexes 1 and 2 (derivatives of the piperic acid), i.e. Pipericcarboxylate triphenyltin [Ph_3SnO_2C-$(CH=CH)_2$-$C_7H_5O_2]_n$ and {[n-Bu_2SnO_2C-$(CH=CH)_2$-$C_7H_5O_2]_2O\}_2$ were most active against all cancer cell lines. These compounds were also active against 3T3 normal cell line, but the IC_{50} values were high as compared to cancer cell lines [215].

10. Conclusions

In this review, We show among the millions of servey research studies that black pepper possesses a potential in both traditionnal and modern medicine as well as in food. The black pepper is miraculously really the King of species due to very rich source of a wide variety of chemical constituents, most of which are biologically active. The long practice of using pepper in different traditional systems of medicine made its scope from the kitchen, to drugs, to cosmetics, merited at early time to impose attention in agriculture and economy. Modern experimental research discovered numerous components : aromatics, aroms, pungents … volatile constituents, monoterpenes, sesquiterpenes, and specially piperin on the different biological activities reveals the significance of its use in traditional systems of medicine. The pepper's use in treating cancer, obesity, hypertension, diabetes, diarrhea, and its bioavailability signifies its attraction in the future. Biotechnology approach is one of the most promising technologies to be used to improve black pepper production and protection. Selected varieties and good agricultural practices should be implemented to improve the productivity of black pepper. The most common pathogens of black pepper are fungus (*Phytophthora capsici*, *Colletotrichum gloeosporioides*), bacteria (*Xanthomonas campestris pv. eticola*) and nematodes. Selected strains of bacteria (*Pseudomonas* sp., *Bacillus* sp.) and fungus (*Trichoderma* sp) demonstrated their effectiveness as biopesticides in this field. During black pepper processing, good manufacturing practices (GMP) should be implemented, according to international standards of FAO/WHO, to control physical, chemical (toxic elements) and microbiological (pathogens) hazards, and to assure high nutritional value of end product.

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