BLACK PEPPER - CHEMICAL COMPOSITION AND BIOLOGICAL ACTIVITIES

Aleksandra N. Milenković[1]*, Ljiljana P. Stanojević[2]

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[1]Scholar of the Ministry of Education, Science and Technological Development of the Republic of Serbia
[2]University of Niš, Faculty of Technology, Leskovac, Serbia

Black pepper (*Piper nigrum* L.) is a tropical plant, best known for its fruit, used as a spice all around the world. The fruits of black pepper can be processed in various ways, so there are end products such as white, black, red, and green pepper. Black pepper contains many substances such as terpenes, alkaloids, lignans, phenylpropanoids, etc., which are responsible for some of the most important biological activities: antioxidant, antimicrobial, anticancer, anti-inflammatory, analgesic, antipyretic, hepatoprotective, bio-enhancing and enzyme inhibitory activities. These activities have also been proven in clinical studies, and probably the future of black pepper research should be based on discovering the most effective way to use the active compounds of pepper for the development of herbal drugs with fewer contraindications than standard drugs. Further preclinical and clinical studies are needed to prepare and apply phytoformulations based on the black pepper isolates.

Keywords: Black pepper (*Piper nigrum* L.), chemical composition, biological activities

Introduction

Family Piperaceae

The Piperaceae family is an ancient family of pantropical flowering plants. This family is known for a large number of species (around 2000), which are grouped into fourteen genera. The Piperaceae family has a significant ethnobotanical and ethnopharmaceutic history. Two genera, including *Piper* and *Peperomia*, represent 90% of all species. The genus *Piper* contains about a thousand plant species, hanging vines, small trees, and shrubs that can be found in humid places around the world (jungles, rainforests, etc.). Some *Piper* spp. used as spices and traditional medicines are of great economic importance for regions like India, Southeast Asia, and Africa [1].

The chemical composition of the genus *Piper* has been studied in detail, and phytochemical studies from around the world have led to the isolation of numerous physiologically active compounds such as alkaloids, amides, propenyl phenols, lignans, neolignans, terpenes, steroids. After isolating the alkaloid piperine from black pepper, the scientists searched for new physiologically active units in the plants of the Piperaceae family, and hundreds of compounds of different classes were isolated. Of particular importance are the biological activities of different types of compounds that show a wide range of pharmacological activities. Also, *Piper* has proven to be a good variety of active substances used in traditional medicine and show excellent results, so they should be supported by clinical treatments and future research [2].

Black pepper –„King of spices"

Known as the „king of spices", black pepper (*Piper nigrum* L.), is a perennial plant and a very important spice in economic and consumer terms. In ancient Egypt, black pepper together with gold and silver was used to mummify the pharaoh's body, due to belief that it was also useful in the afterlife. Written traces of the existence and use of black pepper are found in ancient books such as the Bible, the Qur'an, and the Vedas. According to the Bible, when Queen Sheba visited King Solomon (BC 1015-66) the first gift was a caravan of spices, primarily black pepper. As early as 3000 BC, the Babylonians and Assyrians traded spices, primarily black pepper, with people on the Indian subcontinent. Also, ancient Indian medical texts, such as Ashtangahridaia and Samhitas, mention the use of pepper in rare and unique medical formulations [3].

Black pepper (*Piper nigrum* L.) is the most known species from the Piperaceae family. It originates from the evergreen forests of southwest India and Southeast Asia, commercially grown in tropical regions such as Indonesia, Malaysia, Brazil, Thailand, Madagascar, West Africa [4]. Nowadays, it is widely distributed all over the world, and in Europe regions it is primarily used as a spice [5].

***Author address**: Aleksandra Milenković, Faculty of Technology, Leskovac, University of Niš, Serbia;
Bulevar Oslobođenja 124, 16000 Leskovac,
e-mail: aleksandra.milenkovic@student.ni.ac.rs
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Botanical characteristics

Black pepper is a tropical vine that can grow to a height of 4-9 m, but with the support of other trees. The plant has a shallow root system. The leaves are simple, entire, elliptical, 10-15 cm long and 5-9 cm wide, thick, more or less leathery, and glabrous [4]. The fruit is a drupe up to 8 mm in diameter, better known as peppercorn [6]. The flowers are hermaphroditic, white, and usually 20 to 30 of them are grouped in pendulous spikes. The dried immature fruit of cultivated pepper plants is used as a drug. Black pepper fruit is ball-shaped, 8 mm in diameter, brown with a mesh-wrinkled surface. It has a spicy taste, a specific smell. Chemical constituents of black pepper fruit are given in Table 1. The fruits are collected when their color is greenish-yellow. After harvest, the fruits should be soaked in boiling water for 10 minutes. This provides surface disinfection and starts the fermentation process by giving them a black color. After treatment with boiling water, the fruits are dried in the sun. It takes about 14 days to dry in the sun to achieve a moisture content of approximately 12%. About 35 kg of black pepper fruit can be obtained from 100 kg of green pepper fruit [6]. The blackening of pepper fruit was attributed to the enzymatic oxidation of polyphenolic substrates present in green pepper skin. This kind of process in pepper fruit is similar to the browning of fruits and vegetables known as enzymatic darkening provoked by the enzyme polyphenol oxidase [7].

Table 1. Chemical constituents of black pepper dried fruit (in percentage) [8]

Constituent	Percentage range, %
Moisture	8.7-14.0
Total nitrogen	1.5-2.6
Volatile ether extract	0.3-4.2
Nonvolatile ether extract	3.9-11.5
Alcohol extract	4.4-12.0
Crude fiber	8.7-18.0
Total ash	3.6-5.7
Acid insoluble ash	0.03-0.55

Black pepper – Processing

The ripening period of pepper varies from 5 to 8 months depending on the place of cultivation. In India, crops are harvested during December-January in the plains, and from January to April in the mountains. It is crucial to harvest pepper at the appropriate maturity as the product is considered to have the appropriate organoleptic properties. The fruits are cut by hand and collected in bags when one or two berries in the class turn red or yellow. The harvesting process is expensive, precisely because of handpicking. When the fruit is fully ripe, there is a risk of great losses, either due to the fall of the fruit itself or due to the birds that can ruin the fruit. Therefore, it is very important to accurately determine the degree of maturation of the plant fruit before harvesting, to obtain a good quality end product. Canned green pepper is the final product obtained by putting the pepper fruit in citric acid brine a month before full maturity. Dehydrated green pepper fruits are obtained from unripe pepper fruits, which are blanched in boiling water until the enzymes responsible for blackening the pepper are inactivated and the polyphenols are washed out of the fruits. The fruits are cooled and treated with potassium metabisulfite to retain their green color, then washed again and dried at a temperature not exceeding 50 °C. Black pepper is produced from fully mature, near ripe peppercorns. The peppercorns are boiled briefly in hot water to accelerate the activity of brown enzymes during drying. Before the fruit is fully ripe, the amount of volatile oil and piperine increases, and then decreases during the phase of ripening. The starch content increases during the ripening phase. Red pepper is obtained from fully ripe fruits canned in brine or vinegar. Red pepper can also be dehydrated and its color can be preserved using the previously described method for processing the green pepper. Completely ripe peppercorns are used for the production of white pepper, by removing the outer shell (exocarp, mesocarp) [9].

Table 2. The main chemical constituents of black pepper fruit

	Percentage, %	Reference
Piperine	2-9%	[13]
	3.90%	[14]
	2.6%	[15]
Oleoresin	4.4-12%	[13]
	3.8%	[15]
	2.33-5.67%	[16]
Essential oil	0.4-7%	[13]
	2.81%	[17]
	0.9-1.8%	[18]
Starch	50%	[12]
	28-49%	[13]
	30.4%	[19]
Fatty oils (acids)	1.9-9%	[13]
	5.34%	[20]
	14.41%	[21]

Chemical composition of black pepper fruit

The chemical constituents of pepper can be classified into three major groups: a) compounds that contribute to its spiciness (spicy taste); b) compounds that give a characteristic aroma; c) compounds that make the predominant ingredients (starch), and other compounds, as given in Table 2. The aroma of pepper comes from the essential oil present in the fruit, while the presence of the alkaloids, mainly piperine, is important for its spiciness. Pepper extracts in the form of oleoresins, also containing phenolic compounds, can also be found commercially [10]. Starch may contribute to the cooking and nutritional quality of black peppers. Plant quality is the most important criterion in cultivation when it comes to spices, and pepper is no exception. The quality of pepper is mainly determined by the amounts of piperine, essential oil, or oleoresin [11, 12].

Piperine - the main pungent compound of pepper

Black pepper has a characteristic aroma and spicy taste, which is attributed to piperine (Figure 1) the main alkaloid found in peppercorns. The amount of piperine can be affected by modifications of growing conditions, such as climate or drying conditions and the place of origin. The fruit of black pepper contains piperine in the amount of 2-9% [13]. There are different methods for the isolation of piperine. This yellow-brown substance can be found in the form of crystals and obtained by polar organic solvents by maceration and/or Soxhlet extraction of black pepper fruit [22].

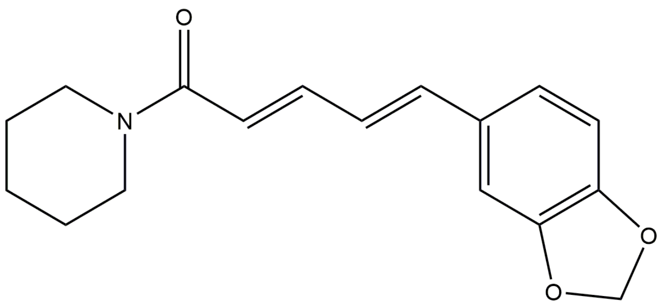

Figure 1 Chemical structure of piperine

Piperine was originally isolated in 1819 by Hans Christian Ørsted. It is a yellow crystalline material of molecular formula $C_{17}H_{19}NO_3$ with a melting point of 128-130 °C. The IUPAC name is (2*E*,4*E*)-5-(2H-1,3-benzodioxol-5-yl)-1-(piperidin-1-yl)penta-2,4-dien-1-one. The solubility of piperine in water is 40 mg/l, while the solubility in organic solvents is much higher (ethanol 1 g/15 ml, ether 1 g/36 ml, chloroform 1 g/1.7 ml). Piperine (Figure 1) is a weakly alkaline substance and depending on whether it is acidic or basic hydrolysis, it can be converted to piperic acid or piperidine [22]. Between the piperidine and 5-(3,4-methylenedioxyphenyl) moieties is the conjugated aliphatic chain representing a "bridge". The structure of alkaloid piperine is particularly suitable for chemical modifications, which can be an advantage in the development of new, different advanced activities [23].

Black pepper contains four isomeric forms: *trans-trans* isomer (piperine), *cis-trans* isomer (isopiperine), *cis-cis* isomer (chavicine), and *trans-cis* isomer (isochavicine). Isomers of piperine have no pungent and spicy taste compared to piperine. Piperine studies have also revealed other alkaloids present in the black pepper fruit such as piperanine, piperettine, piperylin A, piperolein B, and pipericine. The isomerization process intensifies with increasing light intensity and exposure to different weather conditions, and therefore many biological activities can be lost [24].

Black pepper oleoresin

Spice oleoresins range from viscous oils to thick, tacky pastes. They are composed of various components such as essential oils, fixed oils, pigments, pungent constituents such as alkaloids, etc. The components of oleoresin, each in particular, cannot be added directly to food. Oleoresins have high stability and can be stored for a minimum of one year, without any loss in quality. Controlled-atmosphere storage (temperature and humidity) is not required [11].

Oleoresin constitutes around 6% to 13% of black pepper [24]. It is obtained by extraction of black pepper fruit with volatile organic solvents, such as ethanol, acetone, ether, dichloroethane, etc., and subsequent removal of the solvent under reduced pressure to trace levels. The organoleptic properties of black pepper oleoresin are determined by its volatile oil and piperine contents whose abundance depends on the type of pepper and its maturity stage, the used extraction solvent, and the extraction condition. Typically, oleoresin contains 15% to 20% of volatile oil and 35% to 55% of piperine [3].

Essential oil

The black pepper contains about 1%-3% of essential oil, but some studies have shown values of 9% [13]. The essential oil of black pepper is a colorless to yellow-greenish liquid, with a spicy aroma and characteristic odor. The essential oil is obtained by distillation of the dried immature fruits. This essential oil has a specific gravity of 0.860-0.884 and a refractive index of 1.478-1.488 at 20 °C, and the optical rotation range between - 1 ° to - 23 ° so it is characterized as levorotatory [25, 26]. The most abundant compounds in the essential oil of black pepper are monoterpene hydrocarbons, then sesquiterpene hydrocarbons, and also small quantities of oxygenated monoterpenoids and oxygenated sesquiterpenoids [27]. The most common components of black pepper fruit essential oil are presented in Table 3.

Table 3. The most abundant compounds in the essential oil of black pepper fruit

Component	Percentage	Reference
β-Caryophyllene	29.9%	[15]
Limonene	13.2%	
β-Pinene	7.9%	
Sabinene	5.9%	
α-Pinene	4.5%	
Caryophyllene oxide	3.9%	
Terpinen-4-ol	0.7%	
β-Caryophyllene	19.12%	[21]
Limonene	9.74%	
(+)-Camphene	8.44%	
β-Pinene	8.00%	
3-Carene	7.08%	
α-Pinene	6.32%	
3-Carene	29.21%	[28]
D-Limonene	20.94%	
β-Caryophyllene	15.05%	
β-Pinene	9.77%	
α-Pinene	4.69%	
Caryophyllene oxide	0.89%	
Linalool	0.42%	
δ-3-Carene	18.5%	[29]
Limonene	14.7%	
β-Caryophyllene	12.8%	
Sabinene	11.2%	
β-Pinene	6.7%	
α-Pinene	5.6%	
β-Selinene	2.2%	
Terpinen-4-ol	2.0%	
T-Cadinol	0.8%	
Linalool	0.7%	
β-Caryophyllene	23.98%	[30]
Limonene	14.36%	
α-Terpinene	13.26%	
γ-Terpinene	13.26%	
Caryophyllene oxide	8.68%	
Naphthalene	4.19%	
Copaene	3.73%	
Elemene	3.52%	
β-Caryophyllene	26.2%	[31]
σ-Ocimene	5.8%	
α-Pinene	5.5%	
Caryophyllene oxide	4.2%	
α-Copaene	4.2%	
β-Pinene	4.1%	
Limonene	2.1%	

The major components identified by GC/MS analysis of various samples of the essential oils from black pepper fruit are β-caryophyllene (sesquiterpene), limonene, β-pinene, α-pinene, sabinene, 3-carene as well as camphene (monoterpenes) [15, 21, 29, 32]. The main oxygenated terpenes present in the essential oil of black pepper are caryophyllene oxide, linalool, terpinen-4-ol, and eugenol [33]. The chemical structures of the most abundant components in the black pepper essential oil are given in Figure 2. The percentage of components varies widely depending on the origin and variety of the raw material, its stage of maturity, as well as the duration and conditions of storage [33].

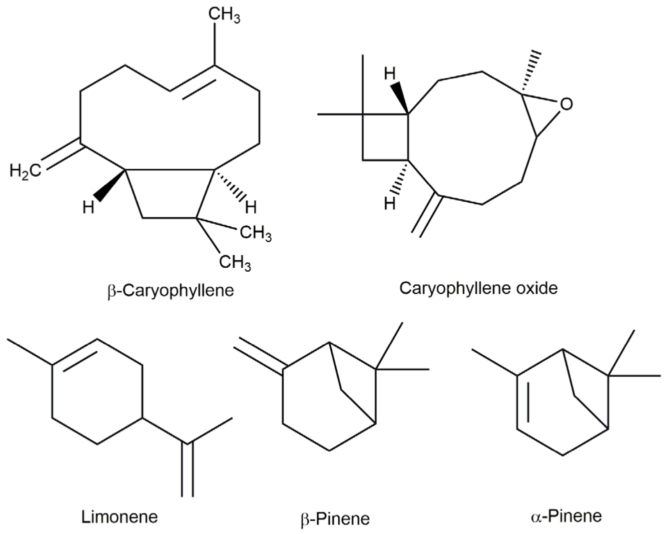

Figure 2 The most abundant components in the black pepper fruit essential oil (ChemDraw)

Other constituents of black pepper

Starch is the main component of black pepper fruit making about 50% of dry weight. Starch can interact with piperine or polyphenols, as well as with other components of the food, changing its nutritional properties [12]. Regardless, there is no much information about the molecular structure of black pepper starch. On the other hand, there is a study that confirms the possibility of a controlled release of piperine from starch nanoparticles that can be potential nanocarriers for piperine [34]. Pepper protein has not been tested in detail, because pepper is mainly used as a spice to improve the aroma of food, and as such it does not contribute to the nutritional value.

Black pepper contains fats in the range of 1.9-9.0%, sometimes about 15%. The most common fatty acids are: palmitic (16-30%), oleic (18-29%), linoleic (25-35%), and linolenic acid (8-19%) [24].

Phenols in black pepper are a mixture of glycosides of phenolic acids and flavanol glycosides. Some of the most abundant phenolic compounds are phenolic acids containing hydroxybenzoic and hydroxycinnamic acids along with significant amounts of quercetin and kaempferol. Flavones that can be found in pepper are: isoquercetin, isoramnetin, 3-*O*-β-D-rutinoside, kaempferol-3-*O*-

arabinoside-7-ramnoside, kaempferol-3-*O*-β-glucoside, and quercetin-3-*O*-β-D-rutinoside. Black pepper also contains sitosterol [24]. The paper of Ali et al. [35], did not show the presence of hydroxycinnamic acids, flavanones, flavonols, and isoflavonoids in the black pepper. There were identified compounds such as 2-hydroxybenzoic acid, apigenin 6,8-di-C-glucoside, 6-hydroxyluteolin 7-*O*-rhamnoside, rhoifolin, scopoletin, hydroxytyrosol, hydroxytyrosol 4-*O*-glucoside, and sesamin [35].

Biological activities of black pepper

Antioxidant activity

Reactive oxygen species are responsible for different undesirable responses of the human body and can cause inflammations, cancer, etc. [36]. Plants, such as black pepper have a good antioxidant potential. Black pepper and its main alkaloid piperine can reduce high-fat diet-induced oxidative stress to the cells and maintain levels of some enzymes (superoxide dismutase, glutathione peroxidase, catalase, glutathione-s-transferase, glutathione) close to the those in the control groups [37]. A few papers have shown that black pepper extracts obtained with the different solvent systems show good antioxidant activity [38, 39]. In a study of Nahak and Sahu [38], it was demonstrated that black pepper ethanolic extract had the best antioxidant activity in all analyzed concentrations compared to aqueous and methanolic extracts. The content of total phenols in black pepper ethanolic extract was almost two times lower than the content of phenols in cubeb pepper ethanolic extract (*Piper cubeba* L.). Cubeb pepper and black pepper originate from the same plant family, black pepper having higher antioxidant activity than cubeb pepper. This indicates that not only phenolic compounds are responsible for the antioxidant activity of black pepper, but also other bioactive compounds that have been extracted, such as some of the alkaloids. It cannot be ruled out that the antioxidant activity of black pepper ethanolic extract may be a consequence of the synergistic effect of phenolic compounds with other biomolecules isolated from the plant material [38].

Comparison of the antioxidant activity of black pepper extracts (water, ethanol, chloroform, ethyl acetate), essential oil, and piperine showed that the essential oil has the highest activity as an antioxidant agent, followed by ethyl acetate extract. Water dissolves macromolecular components such as flavonoid glycosides which have lower antioxidant activity than free flavonoids, which explains the very low antioxidant activity of black pepper water extracts. Based on TLC-bioautography antioxidant results, piperine was qualitatively inactive as an antioxidant [40]. According to Qin et al. [41], piperine showed the scavenging effect on DPPH and ABTS radicals. It is interesting that after structural modifications, piperine derivatives showed higher scavenging capacity on DPPH and ABTS radicals [41]. In a study by Zarai et al. [42], piperine showed the weakest antioxidant activity compared to aqueous, ethanolic, methanolic, and ethyl acetate extracts. At a concentration of 300 μg/ml the degree of neutralization of DPPH radicals with piperine was less than 20%, while at the same concentration the ethanolic extract of black pepper showed a degree of neutralization of about 90%. This is a consequence of the presence of phenolic compounds in the ethanolic extract of black pepper [42].

Antimicrobial activity

The antimicrobial activity of black pepper was reported against a range of bacteria (*E. coli, S. typhi, S. typhimurium, S. aureus, P. aeruginosa, B. subtilis*) and fungi (*F. oxysporum, A. niger, Candida* spp.) [42-49]. It was found that various solvents used for black pepper extraction affect the different susceptibility of the microorganisms. In the study of Khan et al. [43], it was found that black pepper fruit extracts (cold water, hot water, and methanol) show antimicrobial activity against some pathogens. The cold water extract showed the maximum inhibition zone (23 mm) against *E. coli*, while the hot water extract showed the maximum inhibition zone (22 mm) against *S. typhi* and *S. aureus*. The methanolic extract showed an inhibition zone of 21 mm against *E. coli, S. typhi* and *P. aeruginosa* but did not affect *S. aureus* [43].

Furthermore, among various solvent extracts of the black pepper fruit (hexane, dichloromethane, ethanol, and aqueous), the dichloromethane extract showed the highest activity against the bacteria *S. aureus, E. coli, S. typhi* and *B. subtilis* [44]. In contrast, the study by Penecilla and Magno [45], found that n-hexane fruit extract did not show inhibition against *S. aureus, B. subtilis, E. coli*, and *P. aeruginosa* [45].

Two compounds from black pepper, 3,4-dihydroxyphenyl ethanol glucoside, and 3,4-dihydroxy-6-(N-ethylamino) benzamide, were found to inhibit the growth of foodborne pathogens including *S. aureus, B. cereus, E. coli*, and *S. typhimurium*. In the study by Zarai et al. [42], it was found that piperic acid (MIC in the range 78.12-625 mg/ml) showed higher antibacterial activity than piperine (MIC in the range 312.5-625 mg/ml) against many Gram-positive and Gram-negative bacteria. Piperine showed antifungal activity against *F. oxysporum* and *A. niger* [46]. The crude extracts obtained from the black pepper fruit had good anticandidal potential and may be used to treat oral and vulvovaginal candidiasis caused by various species of *Candida* [47].

In the study of Hikal [48], the antibacterial activity of piperine and black pepper oil increased with the concentrations increase. The inhibition effect of piperine and black pepper oil against Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* was noticed, while black pepper oil did not show an inhibition effect against Gram-negative species (*Salmonella sp* and *E. coli*) [48]. Based on the study of Harold [49], the antimicrobial activity of black pepper can be attributed to the presence of the essential oil. The mechanism of action of terpenes has not been fully elucidated, but it is assumed that there is a disturbance in the permeability of the membrane [49].

Anticancer activity

Many studies have proved the anticancer activity of black pepper, especially of piperine, against different cancer cell lines [50]. The ethanolic extract of the black pepper fruit was found to have an anticancer effect on the three colorectal cancer cell lines: HT-29, HCT-116, and HCT-15 [51]. The black pepper extracts (chloroform and petroleum ether extract) of the root showed the cytotoxic effect against human myeloid leukemia HL-60 cells [52]. The methanolic extract of black pepper fruit showed better cytotoxic activity than dichloromethane extract against breast cancer MCF-7, and MDA-MB-231 cell lines [53]. The piperlonguminine, a compound isolated from black pepper fruit showed the cytotoxic effect against breast and colorectal cancer cells [54]. It has been found that some forms of gastrointestinal cancer are significantly reduced during the oral application of piperine. The black pepper ethanolic extract, which contains piperine, acts effectively against lung cancer by altering the reaction of lipid peroxidation [55]. In addition, piperine can limit the cell cycle in the G1/S phase, inhibiting the proliferation and migration of HUVEC (human umbilical vein endothelial cells). In animal models, piperine can interfere with angiogenesis, suppressing tubule formation by endothelial cells and phosphorylation of protein kinase B [56]. It was also found that piperine was active against androgenic and independent prostate cancer cell lines (LNCaP, 22RV1, PC-3, and DU-145), inducing apoptosis by activating PARP-1 (Poly [ADP-ribose] polymerase 1) and caspase-3 [57]. Piperine showed UV absorption between 230 nm and 400 nm with a high molar absorbance at 344 nm, and this UV spectrum covers both UV-A as well as UV-B rays which are the main causes of skin damage and cancer. Accordingly, piperine can be used for cosmetic purposes as a protective factor in sunscreens [58]. It was found that natural bicyclic sesquiterpenes, β-caryophyllene, and caryophyllene oxide present in the essential oil of black pepper possess appreciable anticancer activities, that affect the growth and proliferation of various cancer cells [59]. The other very known monoterpene hydrocarbon present in black pepper essential oil is α-pinene. It increases NK (Natural killer) cell cytotoxicity and can be used in an application for cancer immunotherapy [60].

Anti-inflammatory activity

In a study of Tasleem et al. [61], the anti-inflammatory activity of black pepper and its active compounds based on carrageenan-induced paw edema using a plethysmometer was observed. In this study, piperine showed an anti-inflammatory effect at doses of 10 and 15 mg/kg after 30 min, which lasted for 60 min, while hexane and ethanolic fruit extracts also had activity at a lower dose of 10 mg/kg which lasted for 120 min [61]. Piperine showed the activity in synoviocytes that activate interleukin (IL), inhibiting LPS-stimulated endotoxins (Lipopolysaccharides) [62]. It was also found that piperine reduces the production of IL-6, MMP (Matrix metallopeptidase)-13, and prostaglandin E in the concentration range of 10-100 µg/ml [63]. In addition, the anti-inflammatory potential of piperine was investigated at colorectal sites, inhibiting FFA (free fatty acid) - induced inflammation, mediated by TLR4 (Toll receptor) and ulcerative colitis caused by acetic acid [64]. There are also other alkaloids from black pepper that exhibit anti-inflammatory activity in murine macrophages by inhibiting activation of the NF-kB pathway (nuclear factor kappa-light-chain-enhancer of activated B cells) [65].

The black pepper essential oil showed a very significant result compared to the standard drug Diclofenac. In the case of chronic inflammation induced by formalin, black pepper essential oil caused a 50% inhibition of paw edema at 500 mg/kg while the inhibition by the standard drug Diclofenac at 10 mg/kg was 57.5% [30].

Analgetic and antipyretic activity

Numerous drugs currently used to treat anti-inflammatory disorders are always accompanied by ulcerative effects that cause gastric damage. Piperine was the first amide isolated from the Piperaceae family to have anti-inflammatory properties [66]. Piperine blocks the functions of the oxygenase system, inhibits nonspecific P450 isoenzymes and retains prostaglandin and leukotriene biosynthesis *in vitro* [67].

The study was conducted to evaluate the analgesic effect of piperine in combination with the evaluation of its antipyretic and ulcerogenic effects. The analgesic effect of piperine was determined on experimental mice. Namely, after an intraperitoneal injection of acetic acid, the release of endogenous substances in the peritoneal area caused nerve endings irritation due to the pain response and acute inflammation. Aspirin and other nonsteroidal anti-inflammatory drugs can reduce convulsions in this model by blocking the cyclooxygenase enzyme in peripheral tissues, interfering with transduction at primary afferent pain receptors. Therefore, the analgesic effect of piperine may be due to blocking local prostaglandin levels [67]. This confirms that the analgesic effects of piperine are the result of both peripheral and central mechanisms of action. Antipyretic activity is mainly due to the inhibitory effect on prostaglandin production [68].

Hepatoprotective activity

It was previously determined that methanol extract of black pepper fruit has hepatoprotective properties confirmed in mice with induced liver damage caused by ethanol-CCl_4 [69]. In these experiments, ethanol-CCl_4 was used to increase the levels of triglycerides, alanine transaminase, aspartate transaminase, alkaline phosphatase, and bilirubin. All of these parameters returned to normal after the animals were treated with methanol extract [69]. This extract reduced lipid peroxidation as a hepatoprotective effect at applied doses or in combination with some antituberculosis drugs [70]. In another study, liver damage caused by D-galactosamine in mice was treated with piperine to normalize glutamine oxaloacetate transaminase concentrations and serum pyruvate transaminase levels. The proposed mechanism is associated with decreased hepatocyte susceptibility to TNF (Tumor Necrosis Factor) [71].

Bio-enhancing effect of piperine on drugs

Some drugs show poor oral bioavailability because the drug must not only penetrate the intestinal mucosa but also trigger intestinal enzymes that can inactivate it in the intestinal wall and liver. Piperine is the most investigated compound from black pepper that modulates membrane dynamics and the lipid environment and increases permeability at the site of absorption. The molecular structure of piperine is suitable for enzyme inhibition and inhibits various metabolic enzymes such as cytochrome NADPH (Nicotinamide adenine dinucleotide phosphate), CYP3A4 (Cytochrome P450 Family 3 Subfamily A Member 4), UDP-GDH (Uridine Diphosphate Glucose Dehydrogenase), AHH (Aryl hydrocarbon hydroxylase) and UDPGT (Uridine Diphosphate-glucuronyl-transferase). Inhibition of these enzymes by piperine results in the increased bioavailability of drugs and nutrients such as oxytetracycline, metronidazole, ampicillin, norfloxacin, ciprofloxacin, acefotaxime, amoxicillin trihydrate, curcumin, beta-carotene, carbamate, and carbamine [72]. Piperine is used in combination with antiretroviral drugs to treat HIV-1 infections as well [73].

In the study by Pattanaik et al. [74], an increase in carbamazepine bioavailability was observed after only a single 20 mg dose of piperine [74]. In another study, after treatment of healthy subjects with a piperine dose of 15 mg/day for 3 days in a placebo-controlled crossover study, piperine prolonged the half-life of midazolam and increased the degree and duration of sedation induced by midazolam [75].

With piperine treatment, the half-life of diclofenac was increased by 34%, due to CYP2C9 inhibition, the primary isozyme involved in diclofenac metabolism. Also, the results are consistent with previous research on the effect of piperine on the pharmacokinetics of phenytoin. In healthy subjects and in patients with epilepsy, the use of piperine moderately increased the concentration of phenytoin in plasma [76].

Auti et al. [77], reported that piperine showed significant changes in the pharmacokinetic profile of simvastatin (10 mg/kg), verapamil (10 mg/kg), and senidazole (10 mg/kg) when administered alone and in combination with a fixed dose of piperine (10 mg/kg) [77]. Piperine increased the bioavailability of these drugs by 2.53, 1.55, and 1.08 times [77, 78].

Black pepper as an enzyme inhibitor

A comparative analysis of piperine and antiviral drugs such as hydroxychloroquine and chloroquine yielded results that support the use of piperine. The obtained results indicate the ability of piperine to cause structural changes in viral protease (3CL) with a statistically significant difference in the effects of folding or unfolding of an enzyme ($p<0.001$), using the distances between Arg4 and Gly138 residues as reference values. Based on bioinformatics tools, it was concluded that piperine binds strongly to the 3CL protease COVID-19 compared to chloroquinine and hydrochloroquine, which promotes important structural changes in this viral protease, causing the enzyme to bend and thus reduce its activity. Therefore, phytocompounds such as piperine can be used in the treatment of this type of viral infection with fewer side effects [79].

Piperine can inhibit the activity of both COX (Cyclooxygenase) enzymes, COX-1 and COX-2, so that cocrystallization of piperine with the COX family can be taken to further form a new class of compounds in the treatment of prostaglandin release biosynthesis. Examination of the anti-inflammatory activity of pepper extract and their isolates, based on their inhibition of COX-1 and -2 enzymes *in vitro*, showed that aqueous and methanolic extracts are selective moderate inhibitors of COX-2 enzyme. Studies on the applied dose of piperine revealed that the activity of piperine, as an inhibitor of the COX-2 enzyme, reaches about 100% at a dose of 50 μg/ml [80].

The analysis of LOX (Lipoxygenase) inhibition revealed that the compounds such as piperine, piperonal, piperic acid, and piperonyl acid possess LOX inhibitory activity. Comparing the results of enzymatic tests in equimolar mixtures, it was found that piperonyl acid had a higher inhibitory capacity (79%) than piperic acid (69%), piperonal acid (64%), and piperine (58%) [81]. There is evidence that piperine is a competitive, reversible, and nonselective MAO-A and MAO-B inhibitor (Monoamine oxidase inhibitors A and B). Piperine has been found to bind to several amino acids that are the binding site of MAO-B enzymes, including Tyr326, Tyr435, and Tyr398. Tyr435 and Tyr398 (Tyrosine residues) are part of the aromatic "cage" which is very important for facilitating the process of deamination of MAO-B enzymes. Piperine can be used in the treatment of Parkinson's disease [82]. The inhibitory effect of black pepper extracts was observed in the following CYP (Cytochrome P450) family enzymes: CYP3A4, CYP1A2, CYP2C9, CYP2D6. Piperine, the active component of black pepper has also been shown, albeit in a small number of studies, to inhibit P450 enzymes. Piperine is a non-competitive inhibitor of CYP3A4 and a less potent inhibitor of CYP1A2 and CYP2D6 [83].

Conclusion

Black pepper, perennial climbing vine of the family Piperaceae, is a very rich source of a wide range of chemical ingredients, most of which are biologically active. Pepper has been used since ancient times as a spice, but it has also been used in various traditional medical preparations, as well as in cosmetics. By expanding the research of the composition of black pepper and its biological activities, the importance of the use of these ingredients as alternative herbal medicines was discovered. Piperine, as the main alkaloid of pepper, but also an essential oil rich in mono- and sesquiterpenes, has shown numerous biological activities such as antioxidant, antimicrobial, anti-inflammatory, hepatoprotective activity, etc. Numerous studies have shown that black pepper extracts can inhibit enzymes responsible for the development of very complicated diseases such as Parkinson's disease and others. Piperine is significant in the way that minimal modification of its structure gives more effective derivatives. Besides piperine, phenolic compounds such as kaempferol, quercetin, can be found bound or free in pepper. This review showed only a part of one wide picture of black pepper composition and activity. Given the diversity of bioactive ingredients of black pepper, its future application in the production of phytopreparations for use in the food, pharmaceutical and cosmetic industries, as well as in the production of herbal medicines is ensured.

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Abbreviations

BC – before Christ
GC/MS – Gas Chromatography/Mass Spectrometry
TLC – Thin Layer Chromatography
DPPH – 1,1-Diphenyl-2-Picrylhydrazyl
ABTS – 2, 2'-Azino-Bis-3-Ethylbenzothiazoline-6-Sulfonic Acid
MIC – Minimal inhibitory concetration
HUVEC – Human Umbilical Vein Endothelial Cells
PARP-1 – Poly [ADP-ribose] Polymerase 1
UV, UV-A, UV-B – Ultraviolet (rays)
NK – Natural Killer
IL – Interleukin
LPS – Lipopolysaccharides
MMP-13 – Matrix metallopeptidase
FFA – Free Fatty Acid
TLR4 – Toll receptor 4
NF-kB – Nuclear Factor Kappa-Light-Chain-Enhancer of activated B cells
TNF – Tumor Necrosis Factor
CYP – Cytochrome P450 Family
CYP3A4 – Cytochrome P450 Family 3 Subfamily A Member 4
CYP2C9 – Cytochrome P450 Family 2 Subfamily C Member 9
NADPH – Nicotinamide Adenine Dinucleotide Phosphate
UDP-GDH – Uridine Diphosphate Glucose Dehydrogenase
AHH – Aryl hydrocarbon hydroxylase
UDPGT – Uridine Diphosphate-glucuronyl-transferase
COVID 19 – Coronavirus Disease 2019
COX – Cyclooxygenase
LOX – Lipoxygenase
MAO-A and MAO-B – Monoamine Oxidase Inhibitors

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Izvod

CRNI BIBER – HEMIJSKI SASTAV I BIOLOŠKE AKTIVNOSTI

Aleksandra N. Milenković[1], Ljiljana P. Stanojević[2]

[1]Stipendista Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije
[2]Univerzitet u Nišu, Tehnološki fakultet, Leskovac, Srbija

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Crni biber (*Piper nigrum* L.) je tropska biljka, poznata po svom plodu, koji se koristi kao začin širom sveta. Plodovi crnog bibera mogu se obrađivati na različite načine, pa se kao finalni proizvodi mogu dobiti beli, crni, crveni ili zeleni biber. Crni biber sadrži različita jedinjenja poput terpena, alkaloida, lignana, fenilpropanoida itd., od kojih potiču mnogobrojne biološke aktivnosti poput antioksidativne, antimikrobne, antikancer, antiinflamatorne, analgetske, antipiretičke, hepatoprotektivne aktivnosti, kao i poboljšanje bioraspoloživosti lekova i inhibitornih aktivnosti enzima. Ove aktivnosti su dokazane i kliničkim ispitivanjima i zato bi se buduća istraživanja o crnom biberu trebala bazirati na otkrivanju najefektivnijih načina primene njegovih aktivnih principa za razvoj novih biljnih lekova koji će imati manje kontraindikacija od standardnih lekova. Pretkliničke i kliničke studije su potrebne kako bi se pripremile i primenile nove fitoformulacije na bazi izolovanih aktivnih principa iz crnog bibera.

Ključne reči: Crni biber (*Piper nigrum* L.), hemijski sastav, biološke aktivnosti