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(REVIEW ARTICLE)

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REVIEW: BIOACTIVE INGREDIENTS OF *BLACK PEPPER* (*PIPPER NIGRUM*), AS POTENTIAL CANDIDATES FOR *MONKEY POX* ERADICATION

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ABSTRACT

Pepper is used worldwide in various sauces and dishes. It contains a major pungent alkaloid, piperine, and a potent terpenoid, limonene. These two metabolites have proven highly effective in many interesting pharmacological actions. They are widely used in various traditional medicine systems, such as Ayurvedic medicine, and exhibit diverse pharmacological activities, including antioxidant, antitumor, antiasthmatic, hepatoprotective, anti-inflammatory, anticancer, antiseptic, and other properties. Piperine and limonene have proven highly effective in enhancing pharmacological activities. They also stimulate pancreatic and intestinal enzymes that facilitate digestion. Therefore, we believe that the piperine and limonene contained in *black pepper* would be excellent metabolites to enrich in the fight against *monkey pox*.

The current treatment used against *M-pox* would, according to research, consist of only relieving the symptoms and certain similar infections (see sub-section 3 on symptoms) presented by *M-pox*, but would not be able to completely eradicate it. These are tecovirimat, cidofovir and brincidofovir. And to date, there is no specific treatment, nor scientific literature on the treatment of monkeypox using *black pepper*. The articles available to date focus only and mainly on the virology, epidemiology and existing antiviral treatment against *M-pox*, without mentioning the use of *black pepper* as a

treatment. Thus, research to find a curative treatment and not only a predictive one for the *M-pox* virus is very urgent, and hence the importance of this new approach.

Research Methods: In this bibliographic survey, our approach focused on the literature on *black pepper* and monkey pox. Several results were retrieved from articles, dissertations, and theses addressing this study. These results were retrieved using Google, which was considered our search engine. In short, it was the documentary technique that was used.

Regarding the results, piperine and limonene contained in black pepper have beneficial effects in the treatment of monkey pox, rather than using the vaccine, which is not reassuring.

Keywords: Black Pepper (piper nigrum), Bioactive ingredient, Monkey pox; Eradication.

1 INTRODUCTION

Black pepper, scientifically known as *Piper nigrum*, is a valuable medicinal plant. It is one of the most widely used and well-known spices in the world.

Spices are natural food additives that contribute greatly to the flavor of our food. Since ancient times, they have been used to enhance our food. Spices possess medicinal and nutritional properties; they have been effectively used as one of the most important components in medicine worldwide. They have a beneficial influence on the efficiency of lipid metabolism and as an antibiotic (Ganesh et al., 2014).

It is an evergreen vine cultivated in the tropics. *Black pepper* is used as a food spice for its pungent and aromatic flavor, as well as its flavor-enhancing properties (Mengliang et al., 2015).

Traditionally, *black pepper* seeds are used in the Democratic Republic of Congo as an infusion to purge people with stomach aches, breathing difficulties, and the healing of certain skin wounds. The roots in decoction are used against rheumatism, syphilis, and gonorrhea. The decoction of the stems and leaves as an antidote and against coughs. Mixed with ginger, it produces a sweet drink, used against dysentery, hemorrhoids, constipation, and also as an aphrodisiac. It is also used in perfumery because of its characteristic aroma (Hans; Bindanda, 1993).

There are several species of pepper in the world, including *Piper abalienatum, Piper diffamatum, Piper denudans*, *Piper amalago, Piper edurum*, etc. (Sumathykutty, et al., 1999).

Pepper is a spice native to the west coast of India (Malabar Coast) in the state of Kerala. In the Middle Ages, spices, rare and sought after, were used as currency. This is where the expression "paying in cash (spices)" comes from. Pepper, then considered the king of spices, was once traded for gold and precious stones (Schweiggert, Carle, et al., 2007). Although pepper is no longer considered a luxury product, it remains today the most popular and widely used spice in the world for its aromatic qualities as well as its medicinal properties (Mamatha, et al., 2008).

2 TAXONOMY

Black pepper (*P. nigrum*) belongs to the *Piperaceae* family in the *Piperales* order. It belongs to the *Piper genus*, which consists of over 1,000 species (Kumar, 2010).

- Kingdom: Plants
- Subkingdom: *Trachenobionta*
- Division: *Magnoliophyta*
- Class: *Magnoliopsida*
- Subclass: *Magnoliidae*
- Order: *Piperales*
- Suborder: *Magnolianae*
- Family: *Piperaceae*
- Genus: *Piper*
- Species: *Piper nigrum*

3 BOTANICAL DESCRIPTION

According to the morphological and biosystematic studies of Ravindran (1990), *black pepper* (*Piper nigrum*) is a perennial climbing plant that thrives in shade with trees or on support poles. The glabrous woody vines grow up to 10 m or more in height. The vines are grown with dimorphic branching (orthotropic monopodial branches and plagiotropic sympodial fruiting branches). The orthotropic shoot has indeterminate growth, and the leaf axils produce lateral fruiting branches. In addition, each node of the orthotropic shoot has clinging roots that help the plant climb support trees (Chandy, Pilloi, 1981).

3.1 Roots

The *black pepper* plant has 10 to 20 primary adventitious roots developing from the base of the mature stem (Purseglove et al., 1981). From the taproot, a network of flexible, snarling lateral roots emerges, forming an abundant superficial hair. The secondary roots can reach 50 cm or more in depth (Mengliang et al., 2015).

3.2 Stem

This forms the structure of the plant and does not exceed 4 meters. They support the adventitious roots and generate the secondary branches. The latter bear the inflorescences (Pandya et al., 2012).

3.3 Leaves

The leaves are simple, elongated, and acuminate at the apex. They are alternate, with a grooved petiole 2 to 5 cm long (Figure 1). These leaves vary in length and width, ranging from 8 to 20 cm and 4 to 12 cm, respectively (Purseglov et al., 1981; Silva et al., 2018).

Black pepper contains essential oils in the leaves and seeds, releasing a strong aroma that can reach more than 6 to 8 cm (Mengliang et al., 2015).

3.4 Flowers

They are yellow-green, arranged in a spiral, and appear as a spike containing 20 to 50 flowers (Figure 1). It detaches entirely upon maturation (Mirza et al., 2018).

They have no sepals or petals and are surrounded at their base by four bracts. They have an ovary that occupies the center of the flower, a very short style, and a stigma (Murlidhar, Goswami, 2012). The fruiting spikes vary in length (3 to 15 cm). After 10 to 15 days of emergence from the spike, the first flower appears at the top of the spike and lasts for about 6 to 10 days. The inflorescence is glabrous, and the pendulous spike rises opposite the leaves on plagiotropic branches (Parhasarathy et al., 2007). Wild type flowers are mostly dioecious, but cultivated type flowers are monoecious. Self-fertilization is predominant, and protogyny is also found in black pepper (Sasikumar et al., 1992). The chromosome number of Piper nigrum is 2n = 52. This indicates its balanced tetraploid nature (Jose et al., 1998).

3.5 Fruits and Seeds

The fruits are fleshy, globular berries with a diameter of 4 to 6 mm. The fruits are green in color, but they turn yellow to red and finally black at maturity. *Pepper* fruits appear 9 months after flowering. Each fruit contains a seed (Ayad, 2014). Harvested fruits are sun-dried for later use (Sasikumar et al., 1992).

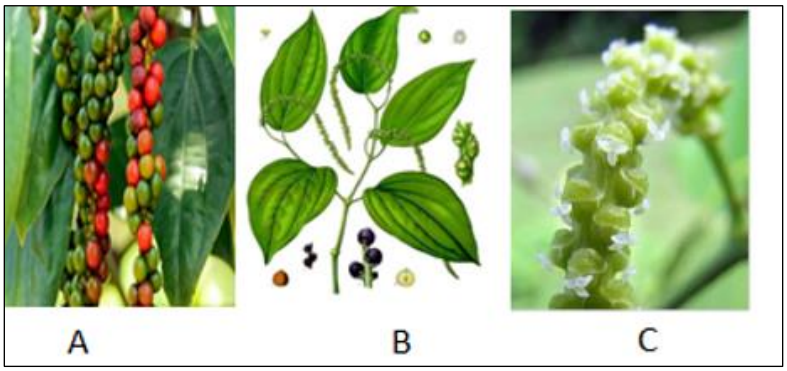

Figure 1: (a) Fruits, (b) Leaves and seeds and (c) Flowers of *Piper Nigrum*

3.6 Habitat and Cultivation

Black peppers grow best in humid tropical climates at ambient temperatures between 25 and 30°C in deep, well-drained soil with good water-holding capacity. It is propagated from dry seeds or from cuttings or runners of established plants (Kumar, Vinay, 2017).

3.6.1 Chemical Composition

Piper nigrum is rich in minerals, vitamins, bioactive metabolites, and nutrients. The chemical composition of 100 g of *black pepper* seeds contains 66.5 g of carbohydrates, 10 g of protein, and 10.2 g of fat (Trainer, Grenis, 2001), as well as a relatively high concentration of minerals such as calcium (400 mg), magnesium (235.8 to 249.8 mg), potassium (1200 mg), phosphorus (160 mg), and lower concentrations of sodium, iron, and zinc (Nwofia et al., 2013; Gurdip et al., 2004; Surya, 2020). These minerals are essential elements in human daily activities. In addition, *black pepper* also has a high concentration of vitamins such as Vitamin C, B1, B2 and B3. *Black pepper* grown in Nigeria had a tannin concentration ranging from 2.11 to 2.80 mg/100 g (Gurdip et al., 2004). In a recent study on black pepper, some researchers reported the presence of flavonoids such as catechin, quercetin and myricetin, and carotenoids, namely lutein and β-carotene were detected in significant concentrations (Gurdip et al., 2004; Sruthi et al., 2013) (Table 1). (Trainter, Grenis, 2001). (Trainter, Grenis, 2001; Nwofia et al., 2013; Gurdip et al., 2004).

Table 1: Nutritional composition in 100g of *Piper nigrum* (Trainer; Grenis, 2001; Nwofia et al., 2013; Sruthi et al., 2013; Surya, 2020; Gurdip et al.,2004).

N°	Nutritional composition		Quantity/unit
1	Organic Compounds	Water	8g
2		Energy	400Kcal
3		Glucides	66.5g
4		Proteines	10g
5		Lipides	10,2
6		Total ash	3.43-5.09
7		Crude fiber	10.79-18.6
8	Minerals	Calcium	400mg
9		Magnesium	235.8-249.8mg
10		Phosphorous	160mg
11		Potassium	1200mg
12		Fer	17mg
13		Zinc	1,45-1,72
14	Vitamins	Vitamin C	27.46-32.53mg
15		Vitamin B1	0.74-0.91mg
16		Vitamin B2	0,48-0,61mg
17		Vitamin B3	0.63-0.78mg
18	Metabolites	Tanin	2.11-2.80mg
19	Flavonoids	Catechines	410µg
20		Myricetine	56 µg
21		Quercetine	13 µg
22	Carotenoids	Luteine	260 µg
23		β-carotene	150 µg

Furthermore, *black pepper* also contains essential oils: oleoresin and piperine (Figure 2).

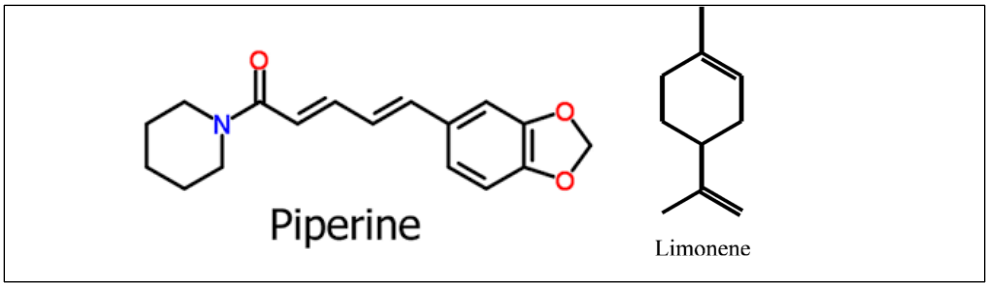

Figure 2: Chemical Structure of Piperine and Limonene

Several researchers have evaluated the essential oils (EOs), oleoresin, and piperine in different parts of *black pepper*. The EO yield from *black pepper* berries and leaves ranged from 1.24 to 5.06% and 0.15 to 0.35%, respectively (Kuriam et al., 2002; Rmili et al., 2014; Utpala et al., 2008). However, oil yield depends on the variety, region, and age of the product, the parts, and the methods used.

Kurian et al., (2002) observed variability in volatile oil and oleoresin content in 14 *black pepper* accessions ranging from 2.7 to 5.1% and 7.6 to 9.4%, respectively. These researchers reported that volatile oil content was positively correlated with oleoresin and suggested that simultaneous improvement of these traits through a simple breeding program is the best tool to improve the quality characteristics of black pepper. Kurian et al., (2002) also reported conventional hydro-distillation as a better method for estimating volatile oil compared to other techniques.

The oleoresin content of *black pepper* varied between 4.27 and 12.73% (Sruthi et al., 2013; Hussain et al.,., 2017), and the characteristic natural alkaloid of *black pepper* "piperine" varied from 2.13 to 5.80% and 0.12 to 20.86%, in seeds and leaves accordingly. Piperine is a pungent alkaloid, in solid form. It is optically inactive and poorly soluble in water. Its molecular formula is C17H19NO3 with a melting point of 128 °C. The amount of piperine varies in plants belonging to the *Piperaceae* family, its content can be influenced by environmental factors (Rachmi, Fakhrurrazi, 2020).

The secondary metabolites found in *Piper nigrum* are divided into three main families: polyphenols, terpenes, and alkaloids (Chen et al., 2020).

3.7 Polyphenols

Constitute a family of organic molecules specific to the plant kingdom. They possess a number of substituted hydroxyl groups or sugars that are polar compounds, generally soluble in polar solvents such as ethanol, methanol, butanol, acetone, etc. (Kapoor et al., 2009). Polyphenols are synthesized in plants at the chloroplast level (Bermawie et al., 2019). They are involved in protecting plants against type B UV radiation and their defense against microbial attacks (Garresh et al., 2014).

3.8 Terpenes

They are mainly found in essential oils and are represented by: Monoterpenes and Sesquiterpenes (Wenxuechen et al., 2018).

3.9 Alkaloids

They are organic, nitrogenous, and alkaline substances of plant origin. They mainly belong to four botanical families: Papaveraceae, Papilionaceae, Ranunculaceae, and Solanaceae. They are used as analgesics (Pennapa et al., 2010).

3.10 Essential Oil, Oleoresin, and Piperine

Several researchers have evaluated essential oils (EO), oleoresin, and piperine in various parts of *black pepper*. The EO yield from *black pepper* berries and leaves ranged from 1.24 to 5.06% and 0.15 to 0.35%, respectively (Kurian et al., 2002; Rmili et al., 2014; Utpala et al., 2014). However, oil yield depends on the variety, region, age of the product, parts, and methods used (Table 2). Kurian et al. (2002) observed variability in volatile oil and oleoresin content in *black pepper*, ranging from 2.7 to 5.1% and 7.6 to 9.4%, respectively.

Table 2: Composition of the main essential oils (EO) from the various parts and origins of *Piper nigrum* (Hussain et al., 2017; Yu et al., 2017; Kumoro et al., 2010; Aziz et al., 2012)

N°	Country of origine	Parts used	Essential oils	Composition en %
1	South India	Seeds	β-caryophyllene	9.52-26.95
2			Limonene	9.52-26.95
3			Sabinene	0.0-19.23
4			α-pinene	3.88-6.48
5			β-bisabolene	1.32-7.96
6			α-humulene	1.11-2.44
7			α-copaene	0.20-5.51
8			α-cadinol	0.18-4.89
9			α-thujène	0.60-2.94
10	South India	Leaves	Nerolidol	0.14-66.32
11			α-pinene	0.12-20.86
12			β-caryophyllene	2.09-9.65
13	Bangladesh	Seeds	β-caryophyllene	18.39
14			α-pinene	16.68
15			Limonene	16.16
16			β-pinène	13.61
17			5-3-carene	9.23
18			β-phellandrene	3.16
19			Copene	3.13
20			1-naphtalénol	3.00
21			β-myrcène	2,89
22	Sri Lanka	Seeds	β-caryophyllene	12.5
23			β-terpenine	19.51
24			Limonene	19.20
25			Sabinene	19.20
26			α-pinène	11.20
27			β-pinene	12.10
28			α β-phellandrene	4.80
29			Myrcene	2.90
30	Malaysia	Seeds	Limonene	29.91
31			β-pinene	19.00
32			β-caryophyllene	14.00
33			α-pinene	7.30
34			5-3-carene	10.61
35			Myrcene	2.60
36			α-phellandrene	2,20
37			Linalool	2.10

38	Brasil	Seeds	δ-3-carene	55.43
39			α-pinene	16.25
40			Sylvestrene	10.67
41			Germacrene	2.17
42			β-myrcene	1.99
43			Isoterpinolene	1.40

These researchers reported that the volatility of oil content was positively correlated with oleoresin and suggest the simultaneous improvement of the quality traits of *black pepper* by simple selection program which must be a better tool for its improvement. Kurian and colleagues (2002) also reported conventional hydro-distillation as a better method for estimating volatile oil compared to other techniques. The oleoresin content of *black pepper* ranged between 4.27 and 12.73% (Sruthi et al., 2013) and the characteristic natural alkaloid of *black pepper*, piperine ranged from 2.13 to 5.80% and 0.12 to 20.86%, in seeds and leaves.

The EO profile of South Indian *black pepper* seeds is mainly composed of β-caryophyllene followed by limonene, sabinene, α-pinene, β-bisabolene, α-copene, α-cadinol, α-thujene, α-humulene; *pepper* leaves were rich in nerolidol followed by α-pinene and β-caryophyllene [38, 41 (Figure 3). Similarly, the seeds of Bangladesh contained the essential oil composed of β-caryophyllene (18.39%) followed by α-pinene (16.68%), limonene (16.16%), β-pinene (13.61%), 5-3-carene (9.23%), β-phellandrene (3.16%), copaene (3.13%), 1-naphthalenol (3.0%) and β-myrcene (2.89%) (Aziz et al., 2012).

Seed EOs from Sri Lanka, Malaysia, and Brazil showed some notable variations in major metabolites. The yield of minor *black pepper* EO contained β-Elemene (1.74%), δ-Elemene (0.60%), α-Cubebene (0.99%), α-Gaiene (0.36%), α-Zingiberene (0.74%), p-Cymene (0.70%), Bicyclogermacrene (0.31%), γ-cadinene (0.65%), γ-trans-bisabolene (1.39%), hedycaryol (0.37%), and germacrene D (0.22%) (Nicolic et al., 2015).

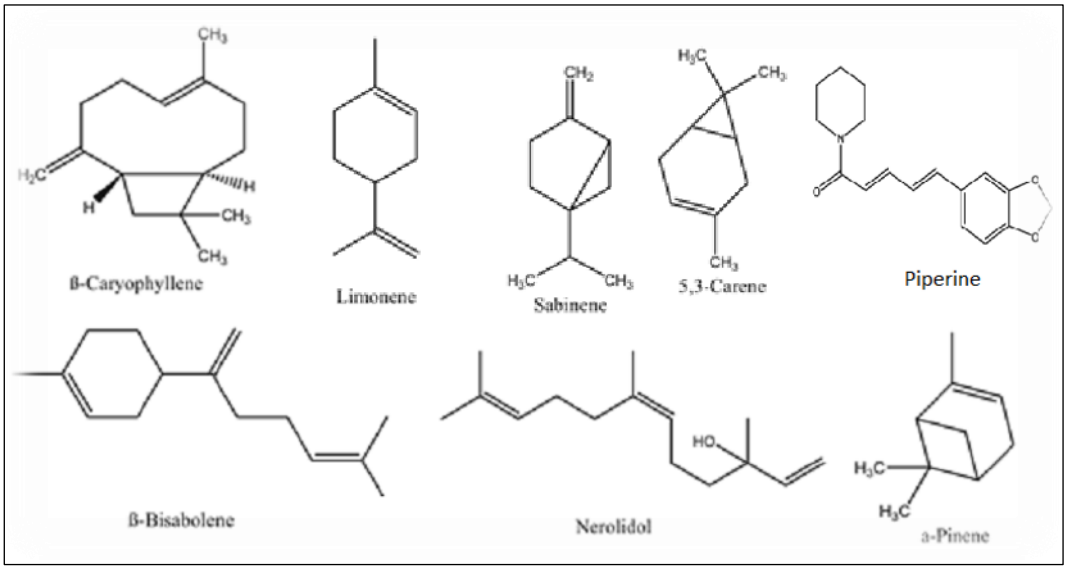

Figure 2: Structures of the molecules contained in the essential oil of *Piper nigrum* (Nicolic et al., 2015).

4 PHYTOTHERAPY

4.1 Black Pepper

Black pepper has been known for its numerous therapeutic properties since ancient times, and its internal and external applications are supported by varying degrees of scientific evidence. This section focuses on its potential therapeutic properties today and the most recent scientific studies to illustrate the modes of action of *Piper nigrum*.

4.1.1 Cholesterol Lowering and Immune Booster

It improves the digestive process by helping to quickly break down large molecules, especially fat, into simpler, easily digestible molecules. *Black pepper* prevents fat accumulation in the body (Suraj et al., 2020).

4.1.2 Digestive Activity

Black pepper improves digestion by stimulating pancreatic enzymes and significantly reducing food transit time in the gastrointestinal tract, increasing saliva production and gastric secretions (Shiva et al., 2020).

4.1.3 Antimicrobial Activity

Black pepper oil is also useful and has demonstrated strong antibacterial efficacy against pathogenic microbes (Brahma et al., 2014). Overall, *black pepper* has effective antibacterial activity against many pathogens that can cause various infections (Zhang et al., 2020).

4.1.4 Oxidative Activity

Oxidation is an inevitable process that occurs in the body's cells and is accompanied by certain adverse reactions. Reactive oxygen species (ROS) are generally considered the causative agent of various diseases, including cancer, inflammation, atherosclerosis, and aging. The excessive generation of ROS overwhelms the body's defensive capabilities due to oxidative stress.

A wide variety of spices and aromatic plants have been identified, and their bioactive compounds contain molecules with antioxidant capacity, with 0.43 mm of *black pepper* (Brewer, 2011).

In another study, Chavarria et al. (206) found that water and ethanol extracts (75 g/ml) of *black pepper* prevented lipid peroxidation by 95.5% and 93.3%, respectively, in their previous experiments, and the total content of phenolic compounds, which was 54.3 and 42.8 g/mg, respectively, was expected to be inhibited. Polyphenol concentrations were greater than 191 mg/100 g. Antioxidant activity was determined by various in vitro tests, which yielded robust results. It has also been suggested that *black pepper* could be a good source of normal dietary antioxidants. Therefore, the inclusion of these functional components in *black pepper* makes it an excellent option for reducing oxidative stress (Shah et al., 2014).

Its strong hydrogen-donating capacity, metal-chelating ability, and free radical scavenging ability all contribute to these effects. Furthermore, the synergistic effects of piperine with other antioxidants such as curcumin make *black pepper* beneficial in disease prevention strategies that include ROS and related species. Piperine at a dose of 10 mg/kg/day injected intraperitoneally repaired diabetes-induced abnormalities in Sprague–Dawley rats in research that used the development of diabetes mellitus as a model of oxidative damage. The benefits come from antioxidants, which reduce LDL oxidation by regulating prostaglandin and leukotriene synthesis (Diby et al., 2009). Therefore, *black pepper* has antioxidant potential, but it needs to be further tested in randomized controlled studies. The results of these studies will ensure that *black pepper* and its bioactive components are used as a natural antioxidant (Diby et al., 2009).

4.1.5 Insecticidal Activities

Black pepper possesses insecticidal activities against the European *chafer* (*Amphimallon majale*, *Coleoptera*: *Scarabaeidae*) (Scott et al., 2005). Upadhyay and Jaiswal (2011) noted that a 0.2% concentration of *black pepper* essential oil has potential repellent activity against adults of the major wheat grain storage pest, *Tribolium castaneum*. In one study, some researchers reported that the concentration of *black pepper* essential oil leads to maximum repellent effects at a maximum exposure time against *T. castaneum*. To date, only two studies have been conducted on the insecticidal effects of *BPEO* (Naseem; Khan, 2011). Other researchers claim that *black pepper* alkaloids have the potential to repel insects and rodents.

Many animals are repelled by *black pepper*. It is also said to be effective against houseflies, having the ability to prevent egg laying and the development of *Giardia* and *Entamoeba*. Hence, *black pepper* also has antiparasitic properties against the aforementioned species. *Black pepper* essential oil can also be used to protect cereals from insect damage and prevent worm infestations (Brahma et al., 2014).

4.1.6 Other Activities

For centuries, *black pepper* has been used in traditional medicines to treat cuts and wounds. Piperine induces the bioavailability of the flavonoid linarin in rats by inhibiting *P-glycoprotein*, and it promotes cellular flow during intestinal absorption (Freg et al., 2014). Therefore, piperine is called a natural bioenhancer (Dudhatra et al., 2014). It stimulates a dose-dependent increase in gastric acid secretion and the interruption of gastrointestinal motility (Han, 2011). Oral

administration of piperine activates the liver, pancreas, and digestive enzymes in the small intestinal mucosa (Awen et al., 2010). In view of the above, we have identified two types of *black pepper* metabolites that can be used in the treatment of various diseases in general and *COPD* in particular. These include piperine and limonene, which are magical metabolites of black pepper.

4.2 Piperine

4.2.1 Antimicrobial Activity

Piperine in *black pepper* can significantly reduce the growth of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Salmonella typhi*. *Black pepper* extracts inhibited the growth of bacteria such as *Staphylococcus*, *Bacillus*, and *Streptococcus*. With minimum inhibitory concentrations (MICs) of 125, 250, and 500 ppm, *black pepper* extracts inhibited the growth of bacteria such as *Staphylococcus*, *Bacillus*, and *Streptococcus* (Weerakkody et al., 2010).

4.2.2 Anticancer Activity

It inhibits certain proinflammatory cytokines produced by *tumor* cells, thus reducing the chances of *tumor* progression (Wenxwechen et al., 2018; Shiva et al., 2020).

BPEO and piperine exert activities against several types of cancer. Piperine significantly suppressed tumor growth of androgen-dependent and androgen-independent prostate cancer cells (Sangkutty et al., 2013). Makhov et al., (2012) noted increased anticancer activity upon co-administration of piperine and docetaxel in human prostate cancer. Moreover, piperine induced DNA damage and apoptosis of tumor cells and was a potential therapeutic agent for the treatment of osteosarcoma (Zhang et al., 2015; De Souza et al.,., 2016). Similarly, piperine reduced lung cancer by stimulating protective antioxidant enzymes and reducing lipid peroxidation (Mona et al., 2009).

Based on the above comments, piperine has potential anticancer activities. However, only a few studies have clarified the antitumor potential of piperine and *BPEO*, and these have been conducted solely in animal models. Therefore, future studies should pay attention to the bioactivity of *BPEO* in several human clinical investigations (Mona et al., 2009).

4.2.3 Anti-inflammatory Activity

Piperine has been found to significantly inhibit the production of two important proinflammatory mediators, IL-6 and PGE. Inhibition of PGE production is important due to its central role in triggering pain (Shiva et al., 2020).

Inflammation can lead to the growth of cancer cells. Inflammation is linked to a variety of diseases such as *arthritis*, *Alzheimer's* disease, *Parkinson*'s disease, and even cancer. Functional elements of diets can have anti-inflammatory properties. Inflammatory flare is a term used to describe a sudden increase in inflammation. Several methods, including inhibition of enzymes involved in the inflammatory cascade (Mueller et al., 2011), are used to combat inflammation (Monica et al., 2010). Recent pharmacological research at the animal and cellular levels has revealed that piperine, one of the active compounds in black pepper, may be effective in combating negative reactions.

The anti-inflammatory properties of *black pepper* were first documented about two decades ago. According to Mujumdar et al. (1990), piperine acts by activating the pituitary-adrenal axis, which helps reduce acute inflammation. Bang et al. (2009) used in vitro studies to further enhance the anti-inflammatory properties of piperine (20 and 100 mg/kg/day). Interleukin inhibition, matrix metalloproteinase inhibition, prostaglandin E2 inhibition, and activator protein 1 inhibition have been proposed as potential anti-inflammatory properties. Hepatoprotective activity

The piperine contained in *Piper nigrum* prevents the increase in GPT and GOT levels in the blood, and this inhibitory effect is mediated by a decrease in the sensitivity of liver cells to tumor necrosis factor (Gurdip et al., 2004).

4.2.4 Antipyretic Activities

Pepper piperine was previously known to possess antipyretic properties (Gurdip et al., 2004).

4.2.5 Cosmetic Activity

Cosmetic use of piperine, a natural bioactivator that improves the permeability of active compounds through the skin, has been reported to stimulate the skin's natural ability to absorb nutrients (Kapoor et al., 2009).

4.2.6 Cytotoxicity Activity

BPEO and piperine have good potential to increase the efficiency of *tumor necrosis factor* (TNF)-mediated apoptosis in breast cancer cells. (Greenshields et al., 2015) reported that a combination of piperine and γ-radiation had higher

cytotoxicity and efficacy in stopping the growth of tripe-negative cancer cells than radiation alone in immunodeficient mice.

Although the safety of piperine and BPEO has been demonstrated, the use of cell lines solely in in vitro tests limits the therapeutic relevance of this result.

4.3 Limonene

Limonene offers many interesting properties. However, it is important to note that to date, most studies have been conducted in vitro. Few studies have been conducted directly on humans. This does not exclude the measured effects of limonene. It is also important to note that this or that property depends more on D-limonene, which is found in citrus fruits, or L-limonene in pine, turpentine. Limonene is a monoterpene with the molecular formula C10H16, characterized by a single ring structure. Limonene is a monoterpene that is cyclohex-1-ene substituted by a methyl group at position 1 and a prop-1-en-2-yl group at position 4 respectively. It has a role as a human metabolite.

It's a cycloalkene and a p-menthadiene (https://pubchem.ncbi.nlm.nih.gov/compound/Limonene) (Figure 2).

4.3.1 Antiseptic, Antiviral Activity

Limonene has antiviral activity on herpes simplex virus but not on the fever virus. It has shown potential action on COVID-19.

4.3.2 Activity

Sedative and muscle relaxant, anxiolytic Limonene also acts as a central nervous system depressant.

4.3.3 Behavioral and Physiological Anti-Stress Activity

Administration of D-limonene to rats for one week significantly increased GABA concentrations, decreased glutamate concentrations, lowered corticosterone secretion, and decreased hypothalamic-pituitary-adrenergic activity.

4.3.4 Gastroprotective Activity

This metabolite acts as an *antiulcer* agent, increasing the secretion of gastric mucus and shock proteins (HSP-70).

4.3.5 Anti-inflammatory

Inhibition of interferon gamma and IL-4 production. It is also used as a bronchial anti-inflammatory, useful in asthma by inhibiting cytokines and the production of reactive oxygen species, and by inactivating eosinophil migration.

4.3.6 Mucolytic and Expectorant Activity

When used as a respiratory oxygenator and secretor, limonene increases the kinetics of mucociliary transport in the sinuses. A standardized mixture (Myrtol®) of monoterpenes (d-limonene, 1,8-cineole, alpha-pinene) with antioxidant, anti-inflammatory, antibacterial, secretolytic, and bronchial spasmolytic properties is active in acute and chronic *rhinosinusitis* and *ENT* conditions, *bronchitis*, and chronic obstructive pulmonary disease, and can eliminate the need for first-line antibiotics.

A capsule mixture (Gelomyrtol® forte) containing 20 mg of alpha-pinene, 75 mg of limonene, and 75 mg of 1,8-cineole taken 4 times daily is as effective as 3 x 30 mg of ambroxol in chronic obstructive pulmonary disease (COPD), as effective as cefuroxime and ambroxol treatments in acute *bronchitis*, with good tolerance and improvement of secondary symptoms such as cough, and it reduces the frequency and intensity of acute exacerbations of chronic *bronchitis*.

4.3.7 Anticancer action

Limonene has potential uses in cancer chemoprevention and chemotherapy, detoxifying carcinogens by inducing phase I and phase II enzymes, which inhibits tumor promotion and progression by acting on *p21ras* proteins.

which is involved in tissue differentiation activity. It induces apoptosis, is anti-angiogenic, and anti-tumor, inhibiting malignant cell growth, and also plays a role in preventing skin cancer and reducing chemoinduction of hepatocellular carcinomas (inhibition of *FPTase* activity, inhibition of *P21ras* expression).

D-limonene exhibits anticancer properties, qualifying it as an emerging antineoplastic agent. Limonene is thought to induce apoptosis via mitochondrial death and suppression of cellular mediators.

4.3.8 Hepatoprotective Activity

Both enantiomers (+)-limonene and (-)-limonene are smooth muscle spasmolytics (*guinea pig trachea* and *aorta*).

4.3.9 Lipid-Lowering Activity

Limonene plays a very important role as an intrabiliary gallstone dissolver.

4.3.10 Antimicrobial Activity

Limonene's inhibition of *Staphylococcus aureus* efflux pumps restores the efficacy of gentamicin against methicillin-resistant *Staphylococcus aureus*.

4.3.11 Antidiabetic Activity

Limonene is a potential inhibitor of protein glycation that may contribute to the improvement of secondary complications of diabetes. Combined with aminoguanidine (an inhibitor of *NO synthases*, of the formation of *AGEs* (protein glycation end products), currently being studied in the prevention of vascular complications of diabetes), it is believed to act by stabilizing the protein structure via hydrophobic interactions.

4.3.12 Other Activities

Chirality appears to be a central factor in biological activity. For example, inhalation of (+)-limonene leads to an increase in systolic blood pressure, alertness, and motor agitation, whereas inhalation of (-)-limonene causes an increase in systolic blood pressure without any effect on psychological parameters, as is the case with other odorant molecules (carvone). (https://www.m-2j.com/blog/comprendre-le-limonene/#Une_action_anti-chimique)

Given that research has shown that there is currently no specific treatment for *Monkey-pox*, finding such a treatment would be necessary, hence the rationale for this work.

Pharmacopoeia or traditional medicine has proven itself over the ages to be an important remedy in the search for natural, less expensive, and accessible ways and means, given the exorbitant cost and certain side effects of some modern medicine products.

Research has demonstrated that *black pepper* is a magical plant from a phytochemical point of view. It contains secondary metabolites with very impressive pharmacological properties. In particular, piperine and limonene exhibit significant properties against several infections (Table 3).

Table 3: Infections caused by mpox and the magical pharmacological properties of black pepper secondary metabolites (Morand A. et al., 2017).

Infections caused by *M-POX*	**The magical pharmacological properties of secondary metabolites of *black pepper***	
	Piperine	**Limonene**
1. Skin rashes and ulcerative lesions	Anti viral Antiseptic Anti-inflammatory	Gastroprotective Antiseptic Dermatitis Antiviral Antiulcer Anti-inflammatory Pain reliever
2. Systemic system (high body fever), Headache, fatigue and muscle pain	-central nervous system depressant	Sedative Muscle relaxant Anti-inflammatory Anti-stress Smooth muscle antispasmodic
3. Lymphadenopathy	-Antibacterial -Antiviral	Antibacterial Antiviral

	-Anti-inflammatory	Anti-inflammatory
4. Respiratory infections (cough, respiratory symptoms)	-anti-inflammatory -pain reliever	Expectorant Mycolitic Antibronchial Respiratory oxygenator Secretoletic Antibronchial Cough suppressant
5. Other complications related to the mpox virus (*pneumonia*, ocular complications, psychological after-effects)	antistress anti inflammatory	Anti-anxiety Anti-stress Central nervous system depressant Behavioral and physiological stress reliever Antioxidant Anti-inflammatory Antibacterial Antiviral

5 MONKEY-POX

5.1 History

Monkey-pox, currently referred to as *M-pox*, is an emerging African disease, known since the 2003 epidemic in the United States. It is a zoonosis caused by an o*rthopoxvirus* of the *Poxviridae* family; the same subset to which *smallpox* virus; *vaccinia* virus or *cowpox*, the active agent in the *smallpox* vaccine; c*amelpox* virus; and *monkey-pox* virus belong. *M-pox* virus is a DNA virus that emerged in humans approximately 60 years ago in Central Africa (Chastel C., 2000).

There are two distinct genomic groups (clades) of *Monkey-pox* virus. The West African group (Clade 2) is thought to have lower pathogenicity and human-to-human transmission than the Central African group (Clade 1), which is much more aggressive to humans.

The *M-pox* virus was accidentally isolated in 1958 from non-human primates imported to Copenhagen, Denmark, as the etiological agent of a *smallpox*-like disease.

M-pox was first recognized in humans in 1970 in the Democratic Republic of Congo (DRC) in young boys unvaccinated against *smallpox* who contracted the disease from contact with *monkeys* (Duraffour S. et al., 2016).

5.2 Epidemiology

According to the WHO, in 2022, Africa had 64,728 biologically confirmed cases reported in 105 countries. The American and European regions reported 62% and 38% of cases, respectively. In France, the Public Health Agency recorded 4,043 confirmed cases of infection. A significant decline was noted from the end of September 2022, with 20 cases per week. Virological analyses identified *Mpox* belonging to the West African clade, now referred to as variant II (WHO, 2021).

5.3 Transmission

Disease transmission generally results from contact with secretions from *MPOX*-associated lesions or contact with large respiratory droplets. These two main modes of transmission require close and prolonged contact with an infected individual, making human-to-human transmission less efficient compared to more transmissible diseases, such as *COVID-19* (Martinez D.E. et al., 2023).

MPXV is known to have a very broad host tropism and can infect many different species. With strong cell and tissue tropism, it infects the heart, brain, ovaries, lymphoid tissue, etc. Once inside the body, the *Mpox* virus infects cells through a series of interactions between viral and cellular proteins, including the viral protein *D8L* which binds to the cell surface receptor, chondroitin sulfate. Once bound, the virus enters the cell by fusing with the cell membrane or by endocytosis. Thus, the *Mpox* virus enters the cell, replicates there, then passes into the bloodstream, and spreads to one of the many types of tissues it is capable of infecting (Chastel C., 2000).

5.4 Symptoms

The clinical signs of *M-pox* resemble those of *smallpox*. After an incubation period of 7 to 17 days (8 days on average), the following general signs may be observed: fever, headache, *myalgia*, and a*sthenia*, preceding the rash, which begins 1 to 3 days after the fever, with a rash of the face and upper limbs that spreads to the trunk and lower limbs in a single outbreak. The lesions consist of macules, then papules. The rash may be accompanied by multiple lymphadenopathies, particularly cervical, which are firm and sometimes painful, and involvement of the ocular (*keratoconjunctivitis*), oral, or genital mucous membranes. Complications may occur: skin superinfection, pulmonary, digestive, and neurological involvement, and cause mortality, which can reach 17% (Duraffour S. et al., 2016). The infection is more serious in children and in immunocompromised individuals and during pregnancy because there is possible maternal-fetal transmission with severe forms in the newborn. (Georges A-J et al., 2004).

5.5 Treatment

The current treatment used in the eradication of *Mpox*, according to research, only relieves the symptoms and certain infections (see section 3 on symptoms) presented by *Mpox*, but is not capable of completely eradicating them. These are tecovirimat, cidofovir, and brincidofovir (Figure 4). (Nolen T.L et al., 2016; Huhn, G.D. et al., 2005; (Ligon, B.L., 2004; Jezek, Z., et al., 1986).

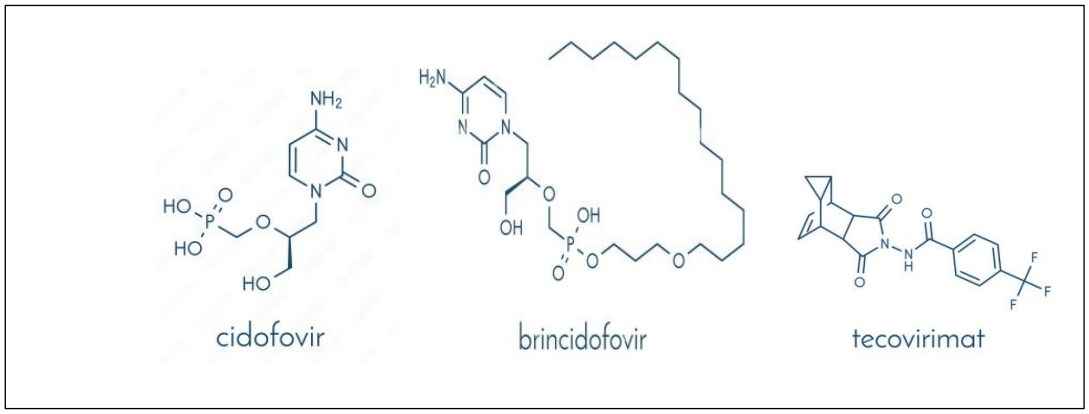

Figure 4: The structures of drugs used to treat some *M-pox* infections (Nolen T.L et al., 2016; Huhn, G.D. et al., 2005; Ligon, B.L., 2004; Jezek, Z., et al., 1986).

5.6 Prevention

Research has shown that *M-pox* and smallpox are two viral diseases that share some similarities but also exhibit significant differences. This is summarized in the table (Table 5) below.

Table 5: Differences and Similarities between *Smallpox* and *M-pox* (Van LS et al., 2022; Morand A. et al., 2017).

Differences		**Similarities**	
Smallpox	***Mpox***	***Smallpox***	***M-pox***
Caused by the *smallpox* virus (*Variola* major and *Variola* minor)	-caused by the *Mpox* virus and member of the same family (*orthopox* virus)	- caused by the same virus family (*ortho poxivirus*)	- caused by the virus of the same family (*ortho poxivirus*)
- Highly contagious and spreads easily between people through the respiratory tract and direct contact	- less contagious and can be transmitted through contact with infected animals and through human contact, but human-to-human transmission is less common	- by direct contact with skin lesions -by air (inhalation of respiratory droplets)	- by direct contact with skin lesions - by air (inhalation of respiratory droplets)
-High fever, fatigue, muscle pain with severe rash and lesions that become scabs	-Similar symptoms but generally milder and the rashes are less severe and sometimes less extensive	-Fever, muscle pain and fatigue, rash that develops into blisters and scabs	-Fever, muscle aches and fatigue, rash that develops into blisters and scabs

-High mortality rate of up to 30% for Variola major	- lower mortality rate approximately 1 to 10% depending on the strains.	-The vaccine developed for *smallpox* offers some protection against *smallpox*	-The vaccine developed for *smallpox* offers some protection against *smallpox*
eradicated through vaccination	- still present with sporadic epidemics, particularly in Central and West Africa		
Widespread vaccination has led to eradication	The vaccine provides protection and its specific vaccination is not widespread		

The vaccines for smallpox eradication are:

- Acam 2000 vaccine, which is a live, attenuated *smallpox* vaccine and can also provide protection against *M-pox*. This vaccine contains:

- Attenuated *vaccinia* virus;
- Additional ingredients: sodium chloride, sodium phosphate, calcium chloride, and preservatives

- Jynneos or imvamune/imvanex vaccine, which is a non-replicating vaccine that is often recommended for at-risk individuals because it has a lower risk of serious side effects:

- Active ingredients: Attenuated vaccinia virus
- Additional ingredients: sodium chloride, sodium phosphate, sucrose, polysorbate 80

- Vaccine based on modern platforms: Research is underway to develop *monkeypox*-specific vaccines using modern technologies such as ARM-messenger vaccines.

- Active ingredients: Messenger RNA
- Lipids: Lipid nanoparticles, lipid cations, cholesterol, phospholipids
- Viral vector vaccine: Active ingredients: Viral vector (such as an *adenovirus*)
- Additional ingredients: Stabilizers such as sucroses or glycerols

Given some similarities between smallpox and Mpox (Table 5), the same vaccines used in the eradication of smallpox are also used "by analogy" in the prevention of *Mpox*. This sufficiently proves that in the same way that we have demonstrated that there is no appropriate treatment or even vaccine in the eradication of *Mpox* to date. Our research in view of the above, demonstrates that the treatment or vaccine used in the "eradication" of Mpox would be erroneous or random because their use in the treatment of *Mpox* is based solely on the similarities between *smallpox* and *Mpox* while these two diseases also have significant differences which are not the least and which should be taken into consideration. Hence, it is imperative and urgent to find a treatment as we have mentioned. This justifies our current research.

6 CONCLUSION

The aim of this research was to demonstrate the use of bioactive ingredients in *black pepper* (*Pipper nigrum*) as potential candidates in the eradication of the monkey pox virus (*M-pox*). *Black pepper* has been a plant with magical properties for centuries. Some (if not all) secondary metabolites of *black pepper* are present in *black pepper*. At the end of this research, a prospective study of the literature showed that this plant has many promising properties that can be used in the treatment of several viral infections, including *smallpox*. We clearly demonstrated, that, to date, *M-pox*, also being a viral infection, has been treated using the same treatments or vaccines used for smallpox, and this in a similar manner, based on the similarities between these two infections (*smallpox* and *Monkey-pox*), without taking into account significant differences between them, which are not the least. This demonstrates that there is no appropriate treatment or vaccine against *M-pox*, and therefore an urgent need to discover or develop and design an appropriate and specific treatment(s) against it.

From this current study and based on the pharmacological properties of the bioactives contained in *black pepper* (particularly limonene, piperine, β-bisabolene, α-copene, α-cadinol, α-thujene, α-humulene, α-pinene, β-caryophyllene, etc.) as demonstrated in this work (using the comparative study in the Table 5), we can strongly conclude that these

bioactives would be potential candidates which could be used in the eradication of *M-pox* viruses in particular and variole in general.

We suggest that pepper could also be used in the treatment of bacterial origin, to combat dermatological diseases. Currently, microbiological and bacteriological researches, as well as screening in general, are underway in our research group and laboratories for other clinical parameters search, such as cytotoxicity.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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