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Review Article

Linum usitatissimum as an antimicrobial agent and a potential natural healer: A review

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Abstract *Linum usitatissimum* commonly known as flaxseed is one of the oldest crops traditionally cultivated mainly for its oil purposes. Flaxseed is widely known for its rich source of nutritive and bioactive compounds. Recently, it has gained considerable interest due to the potential health benefits attributed to its component of metabolites, including its antimicrobial properties. Two main components of flaxseed, the unsaturated fatty acids and lignan, are suggested as the main metabolites that exhibit antimicrobial activities. This paper aims to give an overview on fatty acid and phenolic compound in flaxseed and their possible activities as antimicrobial agents.

Keywords: Alpha linolenic acid; antimicrobial; flaxseed; lignan; phenolic compound.

Introduction

The tremendous and rapid emergence of multiple drug-resistant bacteria has prompted scientists across the world to work on alternative antimicrobial agents. The healthcare system in the 21st century faced such a great challenge to deal with the resistance. Traditional healers use plants for curing and preventing infectious diseases since a long time ago and now modern scientists are trying to duplicate their successes through experimental-based research. Researchers around the world have treasured various phytochemicals which possess inhibitory activities on various kinds of microorganisms *in vitro*. In fact, existing researches have recognized the vital role played by plants rich in various secondary metabolites which have been documented scientifically to exhibit antimicrobial activities (Paiva *et al.*, 2010).

Instead of consuming plants-based food as basic nutrition required by the body, people are now shifting towards food containing health-giving additives known as functional food. Functional foods have been defined with various definitions. According to European Commission's Concerted Action on Functional Food Science (FuFoSE), functional food is defined as food that have a potential good effect on one or more functions of human body beyond the basic nutrition required which can promote health and reduce risk of disease (Doyon and Labrecque, 2008; Bernacchia *et al.*, 2014). Therefore, this review will highlight flaxseed as one of the significant plant-based functional food that has been treasured by the scientific research.

Flaxseed which is also known as linseed is a valuable herb belonging to the *Linaceae* family. *Linum usitatissimum* (*L. usitatissimum)* is the Latin name of flaxseed which brings the meaning of "very useful", and it consists of two basic varieties: golden or yellow and brown (Daun *et al.*, 2003; Bernacchia *et al.*, 2014). It is believed to be originated from Egypt and has been cultivated worldwide for its oil and fibre dated back to many years ago (Kaithwas and Majumdar, 2013). The production of flax was about 3.06 million tons per year and the largest world producer of flax is Canada which recorded 38% of total world's

production (Gutte *et al.*, 2015). Flaxseed is a blue flowering crop with a crispy texture and pleasant nutty taste (Carter, 1993; Gutte *et al.*, 2015). The crop yields small, flat, oval pointed tip seeds with the smooth glossy surface coloured ranging from golden yellow to reddish brown. The spherical fruit capsules consist of two seeds in each of five compartments and the seeds yield fixed oil which is known as flaxseed or linseed oil (Gutte *et al.*, 2015).

The terms linseed and flaxseed are used interchangeably to refer as flax but both of them slightly differ in meaning. The term 'flaxseed' refers to flax when taken as food source by humans whereas linseeds are often referred as flax if it is used for feed and industrial purposes (Morris, 2008; Goyal *et al.*, 2014). Flax was initially introduced as a source of fibre in clothing production (Goyal *et al.*, 2014). Flaxseed oil is among the oldest oil that has been commercialized widely. Interestingly, raw oil is also very useful since it is applied as a constrictive agent in anti-fungal cream and also used as an insecticide and is recorded to exhibit average insecticidal properties (Kaithwas and Majumdar, 2013).

Flaxseed: A potential natural healer

Many researchers have given special attention to flaxseed since the previous studies showed such prominent health benefits including anti-cancer and antibacterial properties (Adolphe *et al.*, 2010). The nutritional and health benefits of flaxseed is highly attributed to its rich composition of omega-3-fatty acid which is incredibly important for human health as well as phenolic compound which promises many health benefits (Hall *et al.*, 2006). In contrast with other foods, flaxseed contains high level of phenolic compounds with extensively rich amount of lignans (Krajčová *et al.*, 2009). Flax lignans, flaxseed oil and fibres have potential health benefits since it is reported to be very helpful in treating many diseases such as atherosclerosis, cardiovascular disease, cancer, diabetes, arthritis, osteoporosis, autoimmune and neurological disorders (Goyal *et al.*, 2014). Recent study reported the presence of huge amount of lignans, dietary fibre and protein in defatted flaxseed meal which is the remnants of flaxseed oil extraction and all of them benefitted human health abundantly (Gutiérrez *et al*., 2010). Another study also reported on the therapeutic efficacy of *L. usitatissimum* oil as an antimicrobial agent in bovine mastitis, a microbial infection which causes inflammatory disorder (Kaithwas *et al.*, 2011).

Fatty acid components in flaxseed

Flaxseed has been studied extensively in diet and disease-related research due to its health benefits related to high content of α-linolenic acid (an essential omega-3-fatty acid), lignans, fibre, proteins, cyclic peptides, polysaccharides, alkaloids, cyanogenic glycosides, cadmium as well as fixed oil (Goyal *et al*., 2014; Shim *et al*., 2014; Chauhan *et al.*, 2015). Previous study found that flaxseeds consisted of 35-45% oil (with linolenic acid and linoleic acid as the major components in oil), 20-25% protein and a small portion of cyanogenic glycosides. The composition of linoleic acid, oleic acid, and linolenic acid were 8-29%, 12-30% and 35-67%, respectively (Coşkuner and Karababa, 2007). However, the composition of flaxseed metabolites may vary accordingly due to several factors such as genetic, environment, seed processing and analytical method (Daun *et al.*, 2003). Alpha-linolenic acid (ALA) is a principal unsaturated fatty acid which plays a vital role in human body as it is essential for the synthesis of extended unsaturated omega-3 fatty acids longer chain, docosapentaenoic acid, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (Baker *et al*., 2016). Unfortunately, both omega-3 and omega-6 fatty acid, linoleic acid (LA) cannot be synthesized from any dietary precursors by human and, hence proper dietary intake of food containing ALA and LA are very crucial to sustain healthy life (Ribeiro *et al.*, 2013). Table 1 summarises the type of fatty acids extracted from flaxseed.

Table 1 Fatty acid composition of flaxseed

Type of fatty acid	Bond	Amount (%) range	
		(Goyal *et al.*, 2014)	(Simopoulos, 2002; Bernacchia *et al.*, 2014)
α-Linolenic acid (omega-3 fatty acid)	C18:3	39.90-60.42	53
Linoleic acid (omega-6 fatty acid)	C18:2	12.25-17.44	17
Palmitic acid	C16:0	4.90-8.00	5
Oleic acid	C18:1	13.44-19.39	19
Stearic acid	C18:0	2.24-4.59	3

Phenolic compounds in flaxseed

Flaxseed is a dietary source from plant that is rich in various kinds of phenolic compounds such as phenolic acids, lignans, flavonoids, tannins and phenylpropanoids (Kasote, 2013). The content of phenolic compound in flaxseed varies mainly due to seasonal effect and the growing location (Oomah *et al*., 1995). Lignans are secondary plant metabolites that are found abundantly in edible plants. Flaxseed is outstandingly rich in lignan secoisolariciresinol diglycoside (SDG) and it was found to be the richest sources of SDG (28 800 – 369 000µg/100g) of any food (Barbary *et al.*, 2010). Lignan constituent of flaxseed make up till 13 mg/g flaxseed (Hall *et al.*, 2006). The other types of lignans found to be present in small amounts are matairesinol, pinoresinol and isolariciresinol (Barbary *et al.*, 2010). Flaxseed lignan is a natural source of important bioactive phytoestrogens that demonstrate a wide range of biological properties. Lignans are secondary metabolites which are synthesized through oxidative dimerization of two phenylpropanoid units (Saleem *et al.*, 2005). The term lignans refers to a group of phenylpropanoid dimers in which the phenylpropane units are connected by the central carbon (C_8) of their propyl side chains (Sarajlija *et al.*, 2012). Lignan compounds belong to dietary phytoestrogen group with important pharmacological activities including antimicrobial (Saleem *et al.*, 2005; Barbary *et al.*, 2010), antitumor (Hirano *et al.*, 1994; Thompson *et al.*, 1996; Herchi *et al.*, 2011), antioxidant (Charlton, 1998; Herchi *et al*., 2011) and antiviral actions (Charlton, 1998). Previous study reported that lignans extraction of flaxseed was optimum using 70% ethanol, at 40ºC temperature, with 28 hours of extraction time (Zhang *et al.*, 2007). Table 2 summarises the amount of lignin precursors extracted from flaxseed.

Table 2 Lignan precursors in flaxseed

Lignan precursors	Amount of lignan precursors (µg/100g)	
	(Milder *et al*., 2005; Gutte *et al*., 2015)	(Barbary *et al*., 2010)
Pinoresinol	871	N/A
Syringaresinol	48	N/A
Lariciresinol	1,780	N/A
Secoisolariciresinol	165,759	28,800-369,000
Matairesinol	529	N/A
Hydroxymatairesinol	35	N/A

Antimicrobial activities of flaxseed

Flaxseed has been associated with various antifungal and antibacterial activities. Many studies associated the antimicrobial activities of flaxseed with the presence of natural polyphenols in general, as well as glucosylated lignans (like SDG or SMG), and aglycones in particular (such as SECO or anhydro-SECO) (Pag *et al.*, 2014; Barbary *et al.*, 2010). Besides that, studies also reported that fatty acids worked on undesired microorganisms by retarding their growth and hence served as the main component of antimicrobial food additives (Freese *et al*., 1973; Zheng *et al.*, 2005). In addition, former studies also revealed that instead of oil and fibres, the residue from the extraction process of flaxseed oil known as seedcake can contribute to the antimicrobial activities since it is associated with high phenolic acids which exhibit antimicrobial properties (Zuk *et al*., 2014). However, to our extent of knowledge, no antiviral studies on flaxseed have been previously reported.

Antifungal activities of flaxseed

Previous studies reported that *L. usitatissimum* exhibited excellent antifungal activities against several types of fungi. These include human pathogenic *Candida albicans*, *Alternia solani*, *Alternia alternata*, *Penicillium chrysogenum* and *Fusarium graminearum*. Previous findings reported that oligosaccharides extracted from flaxseed can control the growth of pathogens such as *Alternia alternata, Alternia solani* and also human pathogenic fungus, *Candída albicans* (Guilloux *et al.*, 2009). This is in accordance with a previous study which reported that *Candida albicans* was highly susceptible towards fixed oil as compared to cefoperazone with the inhibition zone of 10.33 mm and 4.33 mm respectively (Kaithwas *et al*., 2011).

Besides that, flaxseed also has high potential as a good fungal controller in the field of food production and technology since previous studies found that flaxseed demonstrated fungistatic activity capable of regulating the degradation of foodstuffs by the fungi *Fusarium graminearum, Penicillium chrysogenum* and *Aspergillus flavus* (Xu *et al.*, 2008b). Other study reported that lignans extract of flaxseed demonstrated a moderate (ranging from 70% to 90%) antifungal activities at 2.5 to 3.0 mg/ml for both *Aspergillus flavus* and *Aspergillus niger* (Barbary *et al.*, 2010). The noticeable potential of flaxseed as antifungal agent might be due to its rich content of α-linolenic acids and linoleic acid which are suggested to be effective for treatment of fungal infection (Abdelillah *et al*., 2013).

Antibacterial activities of flaxseed

As compared with synthetic antibiotics such as cefoperazone, *L. usitatissimum* fixed oil exhibited good antibacterial activity against a number of microbial strains including *Streptococcus agalactiae* (NCIM 2401), *Micrococcus luteus* (ATCC 10240, ITCC9341), *Staphylococcus aureus* (ITCC8531, ATCC 29737), Bacillus *pumilus* (ATCC 14884), *Enterococcus faecalis* (ATCC 51299), *Bacillus subtilis* (ATCC 6633), *Bacillus brevis* (ITCC7096), *Bacillus cereus* (ATCC 11778) and *Escherichia coli* (ATCC 8739) (Kaithwas *et al.*, 2011). Another study found that flaxseed lignans was less effective against gram negative bacteria such as *Klebsiella sp.* and *Shigella sp.* compared to gram positive bacteria such as *S. aureus* and *Vibrio sp.* (Barbary *et al.,* 2010). In addition, recent studies also documented on the effectiveness of genetically modified flax type (GT) seedcake extracts in combating the growth of *S. aureus* and *E. coli* (Czemplik *et al.*, 2012). Another study has similarly suggested seedcake extract as an alternative to inhibit microbial growth of a wide range and with a partial selectivity (Zuk *et al*., 2014). Table 3 illustrates previous studies on the antimicrobial activities of flaxseed oil.

Table 3 Antimicrobial activities of flaxseed oil

Antimicrobial properties	Type of flaxseed extract / metabolites	Inhibited microorganisms
Antibacterial	(Al-Bayati, 2007)	
	Petroleum ether	*Staphylococcus aureus*
	Ethanol	*Bacillus cereus*
	Petroleum ether	*Klebsiella pneumonia*
	Aqueous	*Pseudomonas aeruginosa*
	(Barbary *et al*., 2010)	
	Lignan	*Staphylococcus aureus cx*
		Vibrio sp.
		Escherichia coli
	(Kaithwas *et al*., 2011)	
	Petroleum ether	*Streptococcus aureus*
		Streptococcus agalactiae
		Enterococcus faecalis
		Micrococcus luteus
		Bacillus pumilus
		Bacillus subtilis
		Escherichia coli
		Lactobacillus sporongenes
		Bacillus brevis
		Bacillus cereus
		Staphylococcus epidermedidis
		Pseudomonas aeruginosa
	(Al-Mathkhury *et al*., 2016)	
	n-Hexane	*Methicillin susceptible S. aureus* (MSSA)
		Methicillin resistant S. aureus (MRSA)
		Staphylococcus epidermis
		Enterococcus faecalis
		Escherichia coli
		Klebsiella pneumoniae
Antifungal	(Guilloux *et al.*, 2009; Kaithwas *et al*., 2011)	
	Petroleum ether	*Candida albicans*
	(Xu *et al.*, 2008a)	
	Flaxseed flour (FF)	*Fusarium graminearum*
		Aspergillus flavus
		Penicillium chrysogenum
	(Barbary *et al*., 2010)	
	Defatted flaxseed powder	*Aspergillus flavus*
		Aspergillus niger

Potential mechanism of action of flaxseed against pathogenic microbes

Recent evidence suggested flaxseed as a good anti-microbial agent. The phenolic compound found in flaxseed induced disintegration of bacterial DNA as well as in inhibiting the gyrase activity (Zuk *et al.*, 2014). An important bacterial enzyme, DNA gyrase belongs to topoisomerases which catalyzes the ATP-dependent negative super coiling of double-stranded closed-circular DNA (Reece and Maxwell, 1991). Various kinds of drugs like antibiotics, antibacterial and anticancer drugs targets DNA topoisomerases as their molecular binding site (Kathiravan *et al*., 2013).

The antibacterial activity of flaxseed lignans is associated with their ability to merge with bacterial cell wall thus, combating bacterial growth (Cowan, 1999; Barbary *et al.*, 2010). Other than that, the existence of long-chain unsaturated fatty acids such as alpha linolenic acid and linoleic acid might contribute to the antimicrobial

therapeutic efficacies of flaxseed. The unsaturated fatty acids have been associated to significantly reduced microbial count based on the previous study reporting linoleic and oleic acids as antibacterial compounds in the herbs (*Helichrysum pedunculatum* and *Schotia brachypetala*) used for wound healing treatment during male circumcision rituals in South Africa (Dilika *et al*., 2000). Normally, antimicrobial action of fatty acid is attributed to long-chain unsaturated fatty acids including linoleic acid, linolenic acid and oleic acid. However, long-chain saturated fatty acids, including stearic acid and palmitic acid, are less active (Seidel and Taylor, 2004).

Existing researches have recognized the potential of unsaturated fatty acid as an antimicrobial agent. However, the actual mechanism of antimicrobial activities is not clear. Previous finding suggests that linoleic acid selectively inhibits an essential component of bacterial fatty acid synthesis known as enoyl-acyl carrier protein reductase (Fab I), an essential component of bacterial fatty acid synthesis. For sustainable microbial growth, the productions of lipid-based components such as cell membrane strongly rely on the synthesis of fatty acid. In addition, unsaturated fatty acids such as linolenic acid, oleic acid, and arachidonic acid also exhibited the inhibition of Fab I. However, Fab I was not inhibited by saturated fatty acid like stearic acid (Zheng *et al.,* 2005). Previous study found that for the antimicrobial assay involving whole cells, saturated fatty acid recorded lesser inhibition compared to unsaturated fatty acids, which is consistent with other findings (Freese *et al.*, 1973). Hence, it can be implied that the antimicrobial activity of *L. usitatissimum* fixed oil is due to the presence of unsaturated fatty acids like linolenic, oleic and linoleic acids present in the oil.

Conclusion

Studies on natural products in search of their antimicrobial potential are becoming more intensified. Previous studies revealed the potential of *L. usitatissimum* as a bacteriostatic and fungistatic agent. Various phytochemical compounds present in *L. usitatissimum* including phenolic compounds and fatty acids have been found to have inhibitory effects on microorganisms. These compounds should be explored *in vivo* to elicit a greater effect to the whole organism systems based on its toxicity, safe dosage as well as its effect on the normal microbiota in the future.

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