A Review: The Emerging Nutraceutical Potential of Pumpkin Seeds

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Abstract

The pumpkin belongs to the family of Cucurbitaceae, is a well-known edible plant that has been frequently used as functional food or herbal medicine. Pumpkins contain rich unsaturated fatty acids, phytoestrogens and vitamins E in their seeds that have potential pharmaceutical, nutraceutical, and cosmeceutical properties. Information regarding their nutritional components and therapeutic properties of pumpkin seeds has expanded dynamically in the recent years and this review focus on the three main components of pumpkin seeds that described before. Several types of unsaturated fatty acids are the dominant component in pumpkin seeds which can play a role in the disease prevention and promote health. Pumpkin seeds also contain the important phytoestrogen compounds, *i.e.*, secoisolariciresinol and lariciresinol that have estrogenic-like effect such as preventing hyperlipidemia and osteoporosis for menopausal women. Phytoestrogens in pumpkin seeds also could be related to a reduced hormone-dependent tumor. Pumpkin seeds are rich in vitamin E contents as an emerging free radical scavenger, anti-aging and antioxidant such as α-tocopherol and γ-tocopherol. Findings of these studies prove that patents field for the innovation product of pumpkin seeds holds promise for the future along with their immense nutraceutical properties.

Keywords : *pumpkin seeds, estrogenic, anticancer, antioxidant, nutraceutical*

INTRODUCTION

Pumpkin (*Cucurbita sp*.) is a fruit vegetable, native to the Western Hemisphere and easily cultivated in Tropical Asia countries such as Indonesia, Malaysia, and Philippines (Tindall, 1983). There are many varieties of pumpkin such as *Cucurbita maxima*, *Cucurbita pepo*, *Cucurbita moschata*, *Cucurbita ficifolia*, and *Cucurbita turbaniformis* in which *Cucurbita moschata* exhibits the widest variation in Indonesia, showed in Fig. 1 (Gemrot, *et al*., 2006). Although the pumpkin itself has various benefits, the pumpkin seeds have been the focus of interest in the last few years in the field of diet and disease research due to the emerging various active components.

Research on pumpkin increases progressively during the last decade, especially focusing on its health benefits. Pubmed recorded more than 200 papers within 2007-2018 of pumpkin and its

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Figure 1. The pumpkin fruit (left) and its seeds (right) commonly cultivated in Indonesia known as *Cucurbita moschata*.

seeds covering on the field of chemistry, biology, pharmacology, and health. Among those of the researches, pumpkin seeds become the focus of interest due to its complexity of the chemical ingredient as well as the health benefits. Pumpkin seeds are highly nutritional and rich nutraceutical components such as unsaturated fatty acids especially palmitic acid, stearic acid, oleic acid and linoleic acid (Stevenson, *et al.*, 2007). Those essential fatty acids are belonging to the ω-6 and ω-3 family which exert amazing nutritional functions and play important role in many metabolic pathways (Miura, 2013). Phytoestrogen supplementation with pumpkin seeds extract has been reported to increase uterine weight, mammary gland, bone density, and prevent hyperlipidemia, the indication of estrogen-like activities in ovariectomized female *Sprague dawley* rats (Gossell-Williams, *et al*., 2008). Pumpkin seeds oil contains rich vitamin E such as α-tocopherol and γ-tocopherol that exhibited positive health effects (Rabrenovic, *et al*., 2014).

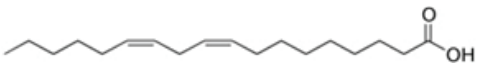
The researchers have so far focused particularly on the three major components of fatty acids, phytoestrogens, and tocopherol in pumpkin seeds oil because they gained attention due to the several health benefits such as antioxidant, anti-inflammation, antidiabetic, anticancer, anti-cardiovascular, anti-hyperlipidemia, and estrogenic-like effect (Table 2). Thus, in this review, we explained more detail about the three major bioactive compounds of pumpkin seeds such as fatty acids, phytoestrogens, and tocopherols as well as to highlight the immense potential effects in the form of roasted, oil and/or extract of pumpkin seeds as the excellent nutraceuticals in the future.

PHYSICOCHEMICAL COMPOSITIONS OF PUMPKIN SEEDS

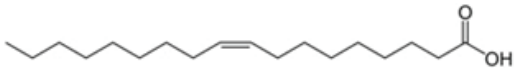
The different species of pumpkin seeds exerts the different components and biological activities (Caili, *et al*., 2006). Many researchers studied the bioactive compositions of pumpkin seeds oil that grown in the different areas of the world. Due to the differences among the species and/or varieties of *Cucurbita spp*., the yield of fatty acids, sterols or phytoestrogens and tocopherols was quite similar to those of each other and belong to the three major components of pumpkin seeds that have been focused by many studies. However, the minor components of pumpkin seeds such as protein, mineral, terpenic alcohol, and fiber also could not be ignored, because they have played role in the synergistic positive effects of pumpkin seeds (Fu, *et al*., 2006). Some technologies are applied to isolate the higher yield of oil from crude pumpkin seeds. Although several studies reported that crude pumpkin seeds extract itself exhibited the broad-spectrum pharmacological effects through *in vitro*, *in vivo* and human trial.

Cucurbita pepo L. is the most popular pumpkin species to be a focus of interest of researches in the world. Recent studies have shown that *Cucurbita pepo* species is rich in polyunsaturated fatty acids such as palmitic acid, stearic acid, oleic acid and linoleic acid, vitamin E like α-tocopherols, γ-tocopherols and carotenoid, phytoestrogens and phytosterols such as daidzein, genistein, secoisolariciresinol, and the trace components. Among those of total percentage of ingredients in pumpkin seeds, unsaturated fatty acids showed the hugest components ranging up to 80%. This value is relatively higher than those reported for peanut seeds oil and soybean seeds oil (Cerny, *et al.*, 1971; Sanders, 1980). The nutrient component in pumpkin seeds is presented in Table 1.

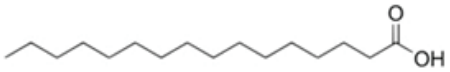
(a) Fatty acids



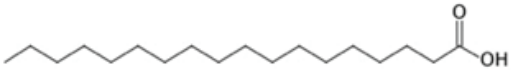
(i) Linoleic acids



(ii) Oleic acids

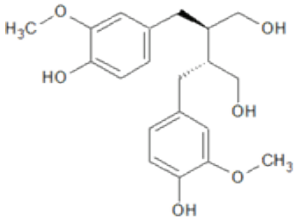


(iii) Palmitic acids

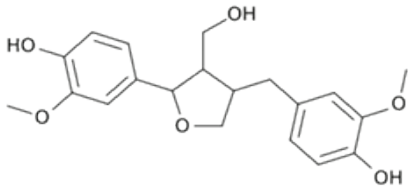


(iv) Stearic acids

(b) Phytoestrogens

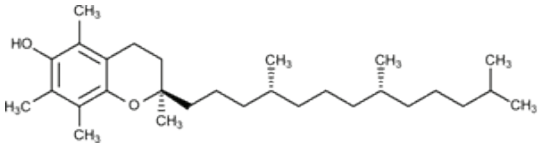


(i) Secoisolariciresinol

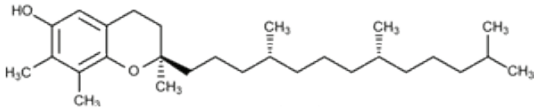


(ii) Lariciresinol

(c) Vitamins



(i) α-tocopherol



(ii) γ-tocopherol

Figure 2. Structures of the major compounds isolated from pumpkin seeds.

The second popular pumpkin species is *Cucurbita maxima* which is cultivated in many areas in the world. Rezig, *et al.* (2012) determined the chemical components of pumpkin seeds and the oil properties from the seeds of *Cucurbita maxima* from Tunisia. They reported that the abundant composition was fatty acids and tocopherol. Another researcher also studied nutritional component of different varieties of *Curcubita maxima* L. var. Berrettina and found that the major fatty acids were oleic acids and the highest components was sterols (Montesano, *et al.*, 2018). Due to the different components among the varieties of Cucurbita grown in the different areas of the world, all studies agreed that pumpkin seeds are a good source of many nutrients.

Table 1. Nutritional components of pumpkin seeds.

Ingredient	Concentration in several varieties			
	Cucurbita pepo L.*)	*Cucurbita pepo* Subsp. pepo Var. Styriaka **)	*Cucurbita maxima* ***)	*Cucurbita maxima*, var. Berrettina ****)
Palmitic acid	9.5-14.5%	10.86%	15.97%	Unquantified
Stearic acid	3.1-7.4%	8.67%	Unquantified	Unquantified
Oleic acid	21.0-46.9%	38.42%	44.11%	41.40%
Linoleic acid	35.6-60.8%	39.84%	34.77%	37.00%
Other fatty acids	<0.5%	Unquantified	Unquantified	Unquantified
α-tocopherols	n.d-91 mg/Kg	882.65 mg/Kg	42.27%	Unquantified
γ-tocopherols	41-620 mg/Kg			Unquantified
Daidzein	5.6-15.3 ng/g	Identified as polyphenol: 66.27 mg/Kg	Identified as polyphenol: 79.6 mg/Kg	Unquantified
Genistein	5.6-15.3 ng/g			Unquantified
Secoisolariciresinol	210 µg/g			Unquantified
Phytosterol	1.6–1.9 %	1.86%	39.60%	63.20%
Protein	25.2–37%	25.40%	33.92%	1.28%
Carotenoid	Unquantified	Unquantified	Unquantified	2.5 mg/L

*) Murkovic, *et al.*, 1996; Murkovic, *et al.*, 2004; Phillips, *et al.*, 2005; Applequist, *et al.*, 2006; Glew, *et al.*, 2006; Sabudak, 2007; Ryan, *et al.*, 2007; Stevenson, *et al.*, 2007
**) Ardabili, *et al.*, 2011
***) Rezig, *et al.*, 2012
****) Montesano, *et al.*, 2018

GENERAL HEALTH BENEFITS DERIVED FROM PUMPKIN SEEDS

In general, pumpkin seeds are an extraordinarily rich source of nutraceutical, pharmaceutical, and cosmeceutical properties that exhibit many pharmacological effects and health benefits. In recent years, *in vitro*, *in vivo*, and pre-clinical studies have proven that pumpkin seeds oil has a wide spectrum of amazing biological activities (Table 2.). Moreover, the presence of high percentage of unsaturated fatty acids, sterols and tocopherol make it an excellent product which could prevent against some diseases (Patel, 2013). The widespread usage of pumpkin seed gains positive acceptance not only as edible oil but also nutraceutical. Not only the therapeutic uses of pumpkin seeds were explored, the safeties of pumpkin seeds against some organs were also tested using several methods. For example, Schiebel-Schlosser and Friederich (1998) found that there were no side effects of Benign Prostatic Hyperplasia (BPH) patients under the treatment of capsules containing 500 mg of a pumpkin seed

Table 2. Some biological activities of pumpkin seeds.

Activity	References
Therapy for arthritis	Fahim, *et al* ., 1995
Antitumor effect	Thompson, *et al* ., 1996
Therapy for irritable bladder	Leung and Foster, 1996
Retarded the progression of hypertension	Al-Zuhair, Abdel-Fattah, and Abdel Latif, 1997
Reduced hypercholesterolemia	Makni, *et al* ., 2008
Free radical scavengers in the heart and kidney	-
Therapy for colon cancer	Awad, von Holtz, Cone, Fink, and Chen, 1998
Possessed estrogenic, antiestrogenic, antioxidative, antiviral, antibacterial, insecticidal or fungistatic	Mazur and Adlercreutz, 1998
Reduced serum cholesterol	Jones, *et al* ., 2000
Treatment of heterophyiasis	Mahmoud, *et al* ., 2002
Immunoregulatory potential	Winkler, *et al* ., 2005
Antiperoxidative properties	Nkosi, *et al.* , 2006
Alleviated diabetes, reliefed of abdominal cramps, and distension due to intestinal worms	Caili, *et al.* , 2006
Therapy for bladderstone disease	Caili, Huan, and Quanhong, 2006
Antioxidant and anti-inflammatory	Kühn, Chaitidis, Roffèis, and Walther, 2007
Therapy for benign prostate hyperplasia	Friederich, *et al* ., 2000; Gossell-Williams, *et al* ., 2006; Fruhwirth and Hermetter, 2007; Hong, *et al.* , 2009; Jiang, *et al* ., 2012; Medjakovic, *et al.* , 2016
Prevented changes in plasma lipids and blood pressure	Gossell-Williams, *et al* ., 2008
Radical Scavenger and inhibit lipoxygenase	Xanthopoulou, *et al* ., 2009
Preventing diabetic complications	Makni, *et al* ., 2010
Increased of reproductive potential	Abd El-Ghany, *et al* ., 2010
Breast cancer prevention and/or treatment	Richter, *et al* ., 2014
Antigenotoxic	Elfiky, *et al* ., 2012; Yasir, *et al* ., 2016

extract. Those research findings have accumulated in the recent years that endorse the wide range of therapeutic values of pumpkin seeds. More clinical trials are required to optimally utilize the nutritional potential of pumpkin seeds.

ESTROGENIC-LIKE EFFECTS

As we know that estrogen hormones play a key role in the menstrual cycle, reproduction, modulation of bone density, and cholesterol transport in the body (Rosano, *et al*., 2007).

Phytoestrogen is a polyphenol compound from plant that exerts mammalian estrogenic-like effect due to the binding ability with estrogen receptor. The oil of pumpkin seeds has proved to contain high percentage of phytoestrogens and sterols such as secoisolariciresinol and lariciresinol (Patel, *et al*., 2012). Sicilia, *et al.* (2003) reported that pumpkin seeds contain secoisolariciresinol approximately 21 mg/100 g of dry weight and Philips, *et al*. (2005) found 265 mg of phytoestrogens/100 g of seeds. Supplementation of pumpkin seeds to rats showed anti-atherogenic and hepato-protective effect in hypercholesterolemic rats (Mazur and Adlercreutz, 1998; Makni, *et al*., 2008). Further study revealed that pumpkin seeds exhibited estrogenic-like effects such as regulating lipid metabolism, bone remodeling, mammary gland and uterus epithelial cells development. Phytoestrogen components were the key role in inhibiting cardiovascular outcomes and balancing the plasma lipids level such as total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (Gossell-Williams, *et al.*, 2008; Jones, *et al*., 2000; Zeb and Ahmad, 2017). In conclusion, phytoestrogens and tocopherols presented in pumpkin seeds contribute to their estrogenic-like effects.

ANTICANCER ACTIVITIES

The previous studies reported that phytoestrogen compounds in pumpkin seeds also exerted an anticancer effect. Some reports showed that pumpkin seeds are a good candidate for cancer prevention and/or cancer treatment. As described in the previous sentences, phytoestrogen compounds are related to estrogen hormones. Thus, several studies explored the association of the effect on estrogen hormone-dependent malignancies, mainly breast cancer. Richter, *et al*., (2013) conducted research about the anticancer effect of pumpkin seeds extract using human breast cancer cells (MCF7), human chorionic carcinoma cell lines (Jeg3 and BeWo), the results showed a cytotoxic effect on those cancer cells and elevated the estradiol production in a concentration-dependent manner. Interestingly, this phenomenon looks to be a contradiction because usually estrogenic-like effect promotes cell proliferation. One of the explanations for this phenomenon is that pumpkin seeds exert a biphasic effect, estrogenic and antiestrogenic activities through different pathways. This phenomenon also found in several phytoestrogen compounds such as genistein and daidzein (Guo, *et al*., 2004). Another *in vitro* result was reported by Medjakovic, *et al.* (2016), they found that hydroalcoholic pumpkin seed extract inhibited not only cancer cells proliferation but also hyperplastic cells, while weaker effects on non-hyperplastic cells. They concluded that the anticancer effect of pumpkin seeds was not mediated through sex steroid hormone receptors. The previous research also claimed that phytoestrogen like isoflavones are considered to exert estrogenic-like effects but possess nonhormonal properties that also may contribute to their effects (Messina and Loprinzi, 2001). Cytotoxic effect of pumpkin seeds ethanolic and aqueous extracts in prostate cancer *in vitro* was conducted by Rathinavelu, *et al.* (2013) and confirmed that the cytotoxic effects of both extracts of pumpkin seeds was mediated through oxidative stress, mitochondrial depolarization and apoptosis mechanisms.

Jiang, *et al.* (2012) reported that there was an inhibition of prostate cancer *in vitro* and *in vivo* experiments in the group treated by pumpkin seeds as a dietary supplement. The animal study using *Sprague dawley* rats showed that the oil from pumpkin seeds inhibited testosterone-induced hyperplasia that would be useful in the management of benign prostatic hyperplasia (Gossell-William, *et al*., 2006). The clinical trial of benign prostate cancer (BPH) patients has proved that after 3-months treatment with pumpkin seed oil, the symptoms were reduced especially in the early stage of cancer (Friederich, *et al.*, 2000; Hong, *et al.*, 2009). In the same study of human trial, a whole extract of Stryrian oil pumpkin seeds was correlated to reduce

benign prostate hyperplasia-related symptoms (Fruhwirth and Hermetter, 2007). Many reports also claimed that the components such as cucurbitacins and moschatin were found in pumpkin seeds and in charge for anticancer activities. Cucurbitacins have been isolated from several species of pumpkin seeds and have been reported to induce apoptosis through JAK/STAT, PARP, MAPK pathways (Rios, *et al*., 2012). Moreover, Xia, *et al*. (2003) reported that moschatin from the mature seeds of pumpkin (*Curcurbita moschata*) inhibited the growth of targeted melanoma cells M21. In general, the molecular mechanism of anticancer effect of pumpkin seeds should be clarified further based on particular concentrations and several types of cancer cells.

ANTIOXIDANT AND FREE RADICAL SCAVENGING PROPERTIES

Pumpkin seeds oil has been proven to contain high antioxidant vitamins like tocopherol and carotenoid by several studies along with sufficient oxidative stability (Xanthopoulou, *et al*., 2009; Seif, 2014; Hernández-Santos, *et al*., 2016). *In vivo* experiment was conducted by Bardaa, *et al*., (2016) using the cutaneous wound healing rats and revealed that oil from pumpkin seeds extracted by cold pressure was better in macroscopic, morphometric and histological data of rat skin than the untreated group. The potent antioxidant effect and protective activity against genotoxic chemicals of pumpkin seeds has performed by Elfiky, *et al*., (2012). Those findings have been consistently and strongly demonstrated that pumpkin seeds oil was accepted as antioxidant and free radical scavenger. Fahim, *et al.* (1995) observed that treatment with pumpkin seeds oil decreased free radicals and was helpful for arthritis. In addition, Yasir, *et al.* (2016) reported that extract of pumpkin seeds exhibited antioxidant and genoprotective effects. Overall, the high amount of tocopherol present in the pumpkin seeds might be considered as playing a protective role against toxic substances and free radicals.

NUTRACEUTICAL POTENTIAL AND FUTURE PROSPECTIVE

In the recent years, pumpkin seeds have a large range of application as a food or herbal medicine. Those waste streams are valuable and can be utilized for food products and/or nutraceutical products. They can be consumed as a snack, salads or breakfast cereal in the roasted form (salted or not). In addition, they could be used in baking as the excellent ingredients of bread or cakes. Moreover, their oil is excellent and could gain acceptance as edible oil and additive component in food, pharmaceutical and cosmetic industries. Pumpkin seeds oil is useful for frying, cooking, baking and salad dressing. Supplement from pumpkin seeds could be developed in the form of a soft capsule. In cosmetic industries, they usually use for skin care products such as anti-aging, free-radical scavenging, skin protection and hair care products such as hair growth stimulants and emollients. The consumption of pumpkin seeds in the oil form or roasted pumpkin seeds is proved to exhibit several positive health effects.

CONCLUSION

The general conclusion of this literature study is that pumpkin seeds have emerging bioactive compositions that promote health and human life. All of these findings bring us to the new idea in developing and innovating nutraceuticals, pharmaceuticals, and cosmeceuticals products from pumpkin seeds for the large range application.

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