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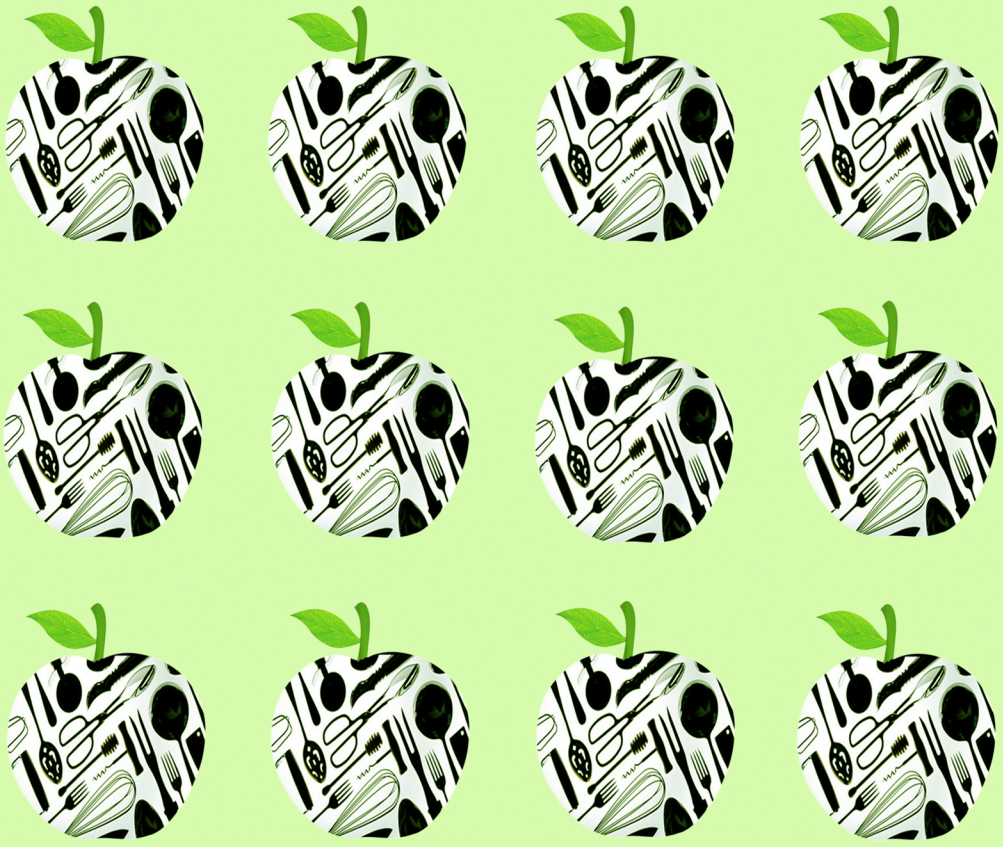

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Editorial

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Maca: Botanical Medicine from the Andes

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Maca (*Lepidium meyenii,* Walp) (Brassicaceae) is a biennial herbaceous plant widely dispersed on high plateaus (altitudes between 4000 and 4500 masl) of the mountains in Peru, particularly in Junin. The underground part of the plant, the tuber, is the main product used for human consumption because of its nutritional value and phytochemical content.[1-3] Maca presents three major phenotypes, yellow, red and black based on their hypocotyl and stem coloration (Figure 1).[4] Andean people use maca as boiled or roasted food, in soups, or to prepare drinks, salads, jams, bread, coffee, substitutes, and even beer.[5,6] A sweet aromatic dessert, called mazamorra, is prepared by boiling the roots in water or milk. A fermented drink, maca chichi, is also made and the dried roots are used to impart a special flavor to the sugar cane rum or aguardiente.[1,7]

Figure 1: Yellow, Red and Black Maca.

Maca is rich in sugars, starch, protein (13-16%), glucosinolates and essential minerals, such as iron and iodine.[1] Maca also contains other compounds such as fatty acids (linoleic, palmitic, and oleic acid mainly), aminoacids (lysine and arginine), many microelements, tannins and saponins. An important component of maca is a mixture of alkaloids known as macaines 1,2,3 and 4 and alkamides (macamides), including alcamide 1 to 5. Some authors suggest that active substances are not just prostaglandins and sterols, but also aromatic isothiocyanates, such as benzyl-isothiocyanate or p-methoxy-benzyl-isothiocyanate to which the aphrodisiac qualities are attributed. Also, the antioxidative activity of maca is linked to those substances.[1,6-8] The main functional properties of maca are shown in table 1.

Maca is an important source of glucosinolates mainly of the aromatic type (glucotropaeolin). Yábar et al.[35] identified six glucosinolates in the yellow, red and black ecotypes. These glucosinolates corresponded to 5-methylsulfinylpentyl, 4-hydroxybenzyl, benzyl, 3-methoxybenzyl, 4-hydroxy-3-indolylm- ethyl and 4-methoxy-3-indolylmethyl. Glucosinolates and their derived products have received scientific attention because of their biological activities, mainly against cancer. The anticancer properties of maca have been also attributed to its flavonoid content. Bai et al.[36] found three flavonoids in maca roots consisting of a tricin unit. Tricin has been considered as a potential cancer chemopreventive agent in humans. A specific study with red maca determined its efficacy on the regulation of prostatic growth by reducing prostate zinc levels in rats. As pointed out by Gonzales et al.[37] the determination of prostate weight and zinc levels can be considered as alternative markers to discriminate the effect of red maca from

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	SUBJECT OF STUDY	MAIN FINDING (S)	SOURCE
REPRODUCTION Male Reproduction:			
Sperm function	Rats	Treatment of rats with maca at high altitude prevented high altitude-induced spermatogenic disruption.	9
	Rats	Maca prevented lead acetate-induced spermatogenic disruption in rats and it may become in a potential treatment of male infertility associated with lead exposure.	10
	Mice	Maca enhances spermatogenesis following spermatogenic damage caused by the organophosphorous pesticide.	11
	Rats	Black maca appeared to have more beneficial effect on sperm counts and epididymal sperm motility.	12
	Men	Maca improved sperm production and sperm motility by mechanisms not related to luteinizing hormone, follicle stimulating hormone, prolactin, testosterone and estradiol.	13
Prostate function	Rats	The hydroalcoholic or aqueous extract of red maca containing 0.1 mg of benzylglucosinolate can reduce prostate size in male rats in which prostatic hyperplasia had been induced by testosterone enanthate.	14
	Rats	Red maca reduced ventral prostate size in normal and testosterone enanthate treated rats.	15
	Rats	Red maca administered orally in rats seems to exert an inhibitory effect at a level post dihydrotestosterone conversion, on the benign prostatic hyperplasia -induced experimentally, although a direct measure of reductase action would still be required.	16
	in vitro	Maca extracts (obtained with different solvents: methanol, ethanol, hexane and chloroform) are not able to regulate glucocorticoid response element activation.	17
Serum hormone	*in vitro*	Maca extracts (obtained with different solvents: methanol, ethanol, hexane and chloroform) are not able to regulate glucocorticoid response element activation. Thus maca does not exert direct androgenic activities.	17
Female Reproduction/Hormonal balance/Menopause	Rats	Serum estradiol levels were not affected.	12,16
	Mice	Progesterone levels increased significantly in mice that received maca, while testosterone levels increased significantly in mice that received maca as well as in those that received both *L. meyenii*Walp and *J. macrantha*. However, there were no marked changes in blood levels of estradiol-17beta or the rate of embryo implantation.	18
	Men	Treatment with maca does not affect serum reproductive hormone levels.	3
	Mice	Administration of aqueous extract of yellow maca to adult female mice increases the litter size and also increases the uterine weight in ovariectomized animals.	19
	Rats	Red and black maca have protective effects on bone architecture in ovariectomized rats without showing estrogenic effects on uterine weight.	20
	Women	These randomized clinical trials demonstrated the favorable effects of maca on menopausal symptoms in healthy perimenopausal, early postmenopausal, and late postmenopausal women. However, the total number of trials, the total sample size, and the average methodological quality of the primary studies, were too limited to draw firm conclusions.	21
OSTEOPOROSIS	Rats	The higher dose of ethanol extract of maca was effective in the prevention of estrogen deficient bone loss.	22
SEXUAL FUNCTION	Rats	Acute and short-term administration of maca produced a small effect of rat male sexual behavior and long-term administration did not increase anxiety.	23
	Rats	Acute and chronic oral administration of maca significantly improve sexual performance parameters in male rats.	24
	Mice and rats	Oral administration of lipidicmaca extract enhanced the sexual function of the mice and rats. as evidenced by an increase in the number of complete intromissions and the number of sperm-positive females in normal mice, and a decrease in the latent period of erection in male rats with erectile dysfunction.	25

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SEXUAL FUNCTION	Rats	Hexanic and methanolic extracts were able to increase mount frequency, while only hexanic fraction significantly improved mount latency. Sub-acute oral administration of hexanicmaca extract improved sexual performance parameters in sexually inexperienced male rats most effectively.	26
	Women	Maca reduces psychological symptoms, including anxiety and depression, and lowers measures of sexual dysfunction in postmenopausal women independent of estrogenic and androgenic activity.	27
	Men	Treatment with maca improved sexual desire.	28
	Men	Small but significant effect of maca supplementation on subjective perception of general and sexual well-being in adult patients with mild erectile dysfunction.	29
VITALITY AND STRESS TOLERANCE	Women	Maca was shown to have significant effects on psychological symptoms including effects on anxiety and depression as measured by the Green Climacteric Scale (GCS) and its subscales.	27
	Mice	The methanolicmaca extract is capable of attenuating or even eliminating variations in homeostasis produced by stress since it reduces or abolishes stress-induced ulcers, elevated corticosterone levels, the reduction of glucose and the increase in the weight of adrenal glands produced by stress.	30
MEMORY & LEARNING	Mice	Black maca presented the better response with respect to latent learning in ovariectomized mice.	31
	Mice	Black maca improves scopolamine-induced memory deficits in male mice.	32
IMMUNITY/NUTRITION	Rainbow trout alevins and juveniles	Maca tuber meal inclusion at least 5% improves growth rate, feed utilization, immunity by increased leucocyte number, and survival of rainbow trout alevins and juveniles.	33
	Rainbow trout juveniles	The results indicate that certain compounds in maca meal have growth enhancing effects in rainbow trout juveniles.	34

Table 1: Main Functional Properties of Maca.

different sources. Flavonoids in maca have shown to be potent inhibitors of monoamine oxidase activity, thus mimicking the actions of monoamine oxidase antidepressant medication. However the specific role of flavonoids in maca remains to be established.[27]

In addition, maca is marketed for its reported benefit in relieving menopausal symptoms, although additional scientific data is necessary to support any efficacy. To this respect,[27] showed the ability of maca to reduce psychological symptoms associated with menopause, including anxiety and depression, along with sexual dysfunction. It is difficult to postulate how maca is acting to reduce psychological symptoms, given the complex nature of psychological control; thus the mechanisms need further investigation.

Regarding the role of maca supplementation in endurance capacity and exercise performance, Stone et al.[38] determined that 14 days supplementation with maca extract significantly improved time to complete a 40 km time trial in trained male cyclists. Thus, the efficacy of maca extract on the improvement of exercise performance was demonstrated. Similarly, supplementation with the lipid-soluble maca extract for 3 weeks increased swimming time to exhaustion in weight- loaded forced swimming rats that can be partially explained by attenuation of exercise-induced oxidative stress.[39]

Maca is also known for its supportive effect on fertility and enhancing and aphrodisiac properties.[6,27] Some studies reported the beneficial effects of maca in sexual function of mice and rats. Ethanol maca extract enhanced the sexual function of the mice and rats, as evidenced by an increase in the number of complete intromissions and the number of sperm-positive females in normal mice. Also, a decrease in the latent period of erection in male rats with erectile dysfunction was observed.[25] Here, the aphrodisiac activity of *L. meyenii* was revealed. Additionally, the hexanicmaca extract improved the majority of the sexual parameters measured such as mount latency in sexually inexperienced male rats most effectively.[26] The effect of maca on fertility has been also supported by Uchiyama et al.[40] They investigated the effect of maca on the serum pituitary hormone levels during the pro-oestrus phase. It was demonstrated that maca uniquely enhances the luteinising hormone (LH) serum levels of pituitary hormones in female rats during the pro-oestrus LH surge and acts in a pharmacological, dose-dependent manner.

As mentioned above, the varieties of maca are based on the root color. Black maca enhanced daily sperm production and increased epididymal sperm motility, in adult rats, compared to red and yellow maca. In relation to the prostate weight, black or yellow maca did not affect it while red maca did reduce the weight. Thus, black maca appeared to have more beneficial effect on sperm counts and epididymal sperm motility than red and yellow maca.[12] In a similar study, Rubio et al.[10] determined that maca reduced the harmful effect on daily sperm production caused by lead acetate treatment. Consequently, maca may become a potential treatment of male infertility associated with lead exposure. The acetate fraction of the hydroalcoholic black

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maca extract was also found to have the greatest effect in spermatogenesis in rats. As cited by the authors, antioxidant components could also play a role in the effect of increased epididymal sperm concentration.[41]

On the other hand, no increase in testosterone levels was observed in healthy men after 12 weeks of maca administration. Further studies are needed to determine the effect of maca administration in subjects with sexual dysfunction.[3] Even tough, maca treatment produced a small effect of rat male sexual behavior, an increase in ejaculation latency and post ejaculatory interval was observed. Also, a long-term administration of maca did not increase anxiety.[23]

Furthermore, maca is recommended for malabsorption syndrome, ethylism, as a laxative, and during reconvalescence, owing to its excellence nutritional characteristics. Also, it is used to combat anemia and insomnia, reduce plasma glucose levels and free fatty acids and as a regulator of female menstruation and menopause.[5,6]

Maca contains several compounds but their specific biological activity and mechanisms of action have not been fully elucidated as yet. Given the maca's compounds potential as anticarcinogenic, antioxidant, performance exercise enhancer among other benefits such as its positive effects on fertility and sexual dysfunction, this plant needs much more intense examination in the future that include human studies. Particularly, continued studies related to glucosinolates in cruciferous vegetables, mainly maca will create more confidence in people whose tendency of healthy eating habits is incessantly growing.

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Research

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Nutritional and Compositional Study of Desi and Kabuli Chickpea (*Cicer Arietinum L.*) Flours from Tunisian Cultivars

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ABSTRACT

Two chickpea cultivars (Kabuli, Desi) were analyzed to determine and compare their physical characteristics, chemical composition and functional properties to one another. The main objective is to promote their use in food applications and open new opportunities for the development of effective techno-functional additives for use in a wide range of food formulations. Significant differences were revealed among the studied cultivars. Kabuli cultivar has significantly shown ($P \leq 0.05$) higher protein content (24.51%), fiber content (21.86%) and lower Water Holding Capacity (WHC) compared to the Desi cultivar. The essential amino acids were present in chickpea seeds except for tryptophan and cysteine. The sulphur-containing amino acid was the first limiting amino acid. The protein solubility-pH profile of chickpea powders revealed a minimum solubility in the pH between 4 and 5 ranging from 14% to 20% for Kabuli cultivar and 17% to 30% for Desi cultivar. Foaming capacity from different chickpea was observed in the range of 36.9-41% and found significantly different ($P \geq 0.05$). Emulsifying Activity (EA) decreased with the increase of flours concentration. Maximum EA (~20%) were observed for Kabuli cultivar. Gelation properties improved when flour concentration increased and the Least Gelation Concentration (LGC) was about 14% for Kabuli cultivar and 16% for Desi cultivar. Chickpea gels were evaluated for their instrumental textural properties. High-quality chickpea flour with improved nutritional properties and good functional properties could beneficially be used in the formulation of food, such as meat, dairy and bakery products.

KEYWORDS: Chickpea cultivar; Physical characteristics; Chemical composition; Functional properties.

ABBREVIATIONS: WHC: Water Holding Capacity; EA: Emulsifying Activity; LGC: Least Gelation Concentration; OHC: Oil Holding Capacity; FC: Foaming Capacity; FS: Foaming Stability; DF: Dietary Fibers.

INTRODUCTION

Chickpea (*Cicer arietinum L.*) is the world's third largest pulse crop based on cultivated area.[1] It is widely cultivated in many countries such as India, Australia, Pakistan and Turkey which are considered as the major world producers.[2] A large number of grown chickpea cultivars have various physical, hydrating, cooking and parching characteristics.[3] According to the color of seed and geographic distribution, chickpea is grouped into two biotypes: Desi (Indian origin) and Kabuli (Mediterranean and Middle Eastern origin) while Kabuli cultivars have large seeds with white to cream colored seed coat, Desi cultivars have small and wrinkled

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seeds with brown, black or green color.[4]

Chickpea is considered as healthy vegetarian food due to its beneficial nutritional profile and medicinal properties.[5] Indeed, the chemical composition of chickpea flour shows that the seed is a good and inexpensive source of proteins, dietary fibers, carbohydrates and vitamins.[6] Chickpea protein quality is superior to other legumes such as pigeon pea, black gram and green gram.[7] From the medicinal standpoint, earlier studies have reported that chickpea seeds are used for the treatment of bronchitis, liver and skin diseases and inflammation of the ear.[8,9] Chickpea is also considered as a hypocholesterolemic agent.[10] Thus, chickpea flour has been proven to play an important role in health problems such as hypertension. Besides, as reported by Ghribi et al.[11] polysaccharides from chickpea were found to have ACE inhibitory activity.

Functional properties, including solubility, water and oil holding capacity, foaming capacity and stability, emulsifying activity and gel formation are not only important in the preparation, processing and storage behaviour of food systems, but also they affect the sensory, nutritional and textural attributes of end products.[12-15] Currently, the whole or partial flour from different legume sources have been added in many food formulations, resulting in increased water holding capacity and yield as well as decreased cooking losses.[16]

In Tunisia, chickpeas are grown primarily for their roles in human food and soil fertility improvement. Tunisia produced nearly 7,505 tons of chickpea in 2009.[17] This production is subject to fluctuations depending on various factors such as essentially environmental conditions.[18] Due to the local demand, Tunisia has become a net importer of chickpea. The largest part of the needed chickpea seeds is imported from Canada. The imported quantity rose from about 4,540 tons in 2002 to 60,402 tons in 2010.[17]

Despite the existence of published works.[16,5,19] describing the chemical and nutritional composition of chickpea, information about Tunisian cultivar is lacking. Thus, the present study is investigated not only to characterize Tunisian chickpea cultivar but also to explore the technological properties for the effective application of flours in many food formulations as meat products to reduce fat content. Moreover, to the best of our knowledge, only a few studies have investigated the properties of whole legume flour. In fact, the tested legume flour was usually prepared after removing lipids and kernel skin.

MATERIALS AND METHODS

Materials

Five kilograms of seeds of each chickpea (*Cicer arietinum L.*) cultivar (Kabuli, Desi) were bought from the local market of Sfax, Tunisia. The seeds were cleaned by distilled water to remove dirt and then dried in room temperature (104 ºF). Next, they were stored in an opaque container at room temperature until laboratory use.

Seed characteristics: physical and cooking properties

Seed weight, volume, density, hydration capacity, hydration index, swelling capacity and swelling index were evaluated according to the method of Singh et al.[20]

Three random samples of 100 seeds from each cultivar per replication were weighed and the values were converted to grams per 100 seeds. The seed volume was determined by transferring 100 seeds into a 100 ml measuring cylinder with the addition of 50 ml of distilled water were added. The gain in volume was taken as the volume occupied by the seed. Concerning the seed density, it was calculated as seed weight divided by seed volume. As for the hydration capacity, it was recorded as gain in weight after overnight (12h) soaking in distilled water. Hydration index was calculated as hydration capacity divided by the original seed weight. While the swelling capacity was determined as gain in volume after overnight soaking in water, the swelling index was calculated as swelling capacity divided by the original seed volume.

For the determination of cooking time, 25 g of seed was added to 250 ml of boiled distilled water. Each 2 min, the samples were tested for their softness according to Zia-Ul-Haq et al.[21] In fact, each seed was pressed between the forefinger and thumb until the disappearance of the white core. The time taken to achieve the desirable softness (disappearance of white core) was recorded as cooking time.

Flour Characteristics

Preparation: Seeds from different chickpea cultivars were ground in blender and passed through sieve (1-2 mm) to obtain flour, which was then packed and stored at 5 ºC until use.

Analytical methods

Dry matter: Dry matter was determined by oven-drying at 105 °C to constant weight.[22]

Ash and mineral content: Ash content was determined by incinerating samples in the muffle furnace at 550 °C for 4 h. Ashes were dissolved in HNO_3[23] and the mineral constituents (Ca, Na, Mg, Mn, Fe, Zn and Cu) were analyzed separately using an atomic absorption spectrophotometer (Hitachi Z6100, Japan).

Total fat content: Crude fat was estimated by Soxhlet extraction with hexane after 8 hours.[22]

Protein content: The total nitrogen was determined by the Kjeldahl method.[24] Protein was calculated using a nitrogen conversion factor of 6.25.[21]

Dietary fibers content: Dietary Fibers (DF) were determined ac-

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cording to the AOAC enzymatic-gravimetric method of Prosky et al.[25] The samples were gelatinized with a heat stable a-amylase (Sigma Chemical Co., St. Louis, MO, USA) for 30 min in a boiling water bath. Then, they were enzymatically digested with protease (Sigma Chemical Co, St. Louis, MO, USA) (60 ºC, pH 7.5, 30 min) to solubilize the protein, followed by incubation with amyloglucosidase (Sigma Chemical Co, Poole, Dorset, UK) (60 °C, pH 4.5, 30 min) to remove starch. After that, samples were filtered, washed (with water, 95% ethanol and acetone), dried and weighed to determine the insoluble fiber. Four volumes of absolute ethanol were added to the filtrate and to the water washings. Then, the precipitates were filtered and washed twice with 80% ethanol and acetone, and the residues were dried and weighed. The obtained values were corrected for ash and protein. The total dietary fiber was determined by summing the insoluble dietary fiber and the soluble dietary fibers.

Carbohydrates content: Soluble sugars content was determined by the phenol-sulphuric acid method[26] with ethanol extraction. Insoluble sugars fraction was submitted to a hydrochloric acid digestion for 2h at 60 °C.

pH: The pH was measured at 20 ºC using an MP 220 pH meter (Mettler-Toledo GmbH, Schwerzenbach, Switzerland).

Water Activity: Water activity was measured at 25 ºC using a Novasina aw sprint TH-500 apparatus (Novasina, pfäffikon, Switzerland).

Soluble solids (Brix): The concentration of soluble solids was determined. A solution of chickpea flour (1000 mg/ml) was previously prepared for Brix determination.[27]

Analysis of amino acid composition: Amino acids were determined by High Performance Liquid Chromatography (HPLC) according to the OJEC standard method.[28] 100 mg of samples were hydrolyzed with 6 N hydrochloric acid in an ampoule containing 0.1% phenol (for the protection of tyrosine) for 24 h at 110 ºC. After acid hydrolysis, 30 ml of citrate buffer (pH 2.2) were added, and the pH was adjusted between 0.5 and 1 with a 7.5 N NaOH and pH 2.2 with a 1 N NaOH. The sample obtained was diluted to 100 ml with citrate buffer after adding 1 ml of a norleucine solution 50 µM (as an internal standard). The sample was filtered through a 0.2 µm nylon filter before being analyze by HPLC. Sulphur-containing amino acids, cysteine and methionine were determined after a pre-hydrolysis oxidation with performic acids. The contents of the different recovered amino acids were expressed g/100 g of protein. The HPLC system (Biochrom) was equipped with an UV-v is detector with two wavelengths, 440 nm and 570 nm, respectively for the proline and the other amino acids, and a cation exchange Waters C18 column (4.6 mm × 200 mm) (XBridegTM, Dublin, Ireland).

Resolution of amino acid derivatives was achieved using a four buffer gradient system. The buffers used were: (A) 0.2 M Na citrate (pH 3.2), (B) 0.2 M Na citrate (pH 4.25), (C) 1.2 M Na citrate (pH 6.45) and (D) 0.4 M NaOH. The buffer was delivered to the column at a flow-rate of 25 ml/h as shown in Table 1.

Functional Properties

Protein solubility: The protein solubility of samples was studied in the pH range of 2.0-12.0. Each sample (100 mg) was suspended in 20 ml distilled water and the pH of the suspensions was adjusted to a specific value. These suspensions were agitated in shaker for 1h at 20 ºC then centrifuged at 8000 g for 15 min. The protein content of supernatant was determined according to Bradford method[29] using Bovine Serum Albumin as standard. Solubility was expressed as the percentage of the total protein of the original sample that was present in the soluble fraction.[30]

Water and oil holding capacities: Water Holding Capacity (WHC) was measured by the method of Sosulski.[31] The sample (3.0 g) was dispersed in 25 ml of distilled water and placed in centrifuge tubes. The dispersions were stirred after the interval of 5 min, held for 30 min, followed by centrifugation for 25 min at 3000 g. The supernatant was eliminated and excess of water was removed by draining for 25 min at 50 ºC and the sample was reweighed.

To determinate Oil Holding Capacity (OHC), the method of Sosulski was used.[31] The samples (0.5 g) were mixed with 6 ml of oil. The contents were stirred for 1 min to disperse the sample in the oil. After a holding period of 30 min, the tubes were centrifuged for 25 min at 3000 g. The separated oil was then removed with a pipette and the tubes were inverted for 25 min to drain the oil prior to reweighing.

The water and oil holding capacities were expressed as grams of water or oil bound per 100 gram of the sample on a dry basis.

Foaming capacity (FC) and Foaming Stability (FS): The capacity and stability of foams were determined according to the method of Lin et al.[32] 50 ml of 3% (w/v) dispersions of sample in distilled water were homogenized at rapid speed for 3 min. The blend was immediately transferred into a graduated cylinder. The volume was recorded before and after whipping.

FC was expressed as the volume (%) increase due to whipping.

$$\textit{Volume increase (\%)} = (V_2\text{-}V_1/V_1)\times 100$$

where V_1= initial volume of solution; V_2= volume of solution after whipping.

For the determination of FS, foam volume changes in the graduated cylinder were recorded at intervals of 10, 20, 40, and 60 min of storage.

Emulsifying properties: Emulsifying Activity (EA) was deter-

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mined according to the methods of Neto et al.[33] 5 ml of flours dispersion in distilled water (10 mg/ml) was homogenized (1 min) with 5 ml oil. The emulsions were centrifuged (1100 g, 5 min) and the height of the emulsified layer and the total contents in the tube was determined.

The emulsifying activity was calculated:

Emulsifying activity (%) = (Height of the emulsified layer/ Height of the total content)×100

The influence of concentration (2-8% w/v) on emulsifying properties of flours was investigated.

Least Gelation Concentration (LGC) and gel texture properties: The LGC was determined by the method of Sathe et al.[34] Test tubes containing suspensions of 2%, 4%, 6%, 8%, 10%, 12%, 14%, 16%, 18%, and 20% (w/v) were heated for 1 h in boiling water and cooled at 4 ºC for 2 h. LGC is the concentration above which the sample does not fall down or slip when the test tube is inverted.

The texture properties of chickpea gels were determined by (Texture Profile Analysis) TPA test. A texture analyzer (LLOYD instruments, Fareham, UK) was used to measure the force-time curve for a two-cycle compression. All measurements were carried out in a controlled room at 25 ºC. A fixed quantity of flours was placed in a plastic food container to have a constant sample thickness (40 mm). A cylindrical probe (19 mm diameter) was used to compress the sample to a 20 mm in depth with a displacement speed of 30 mm/min. Then, the probe was returned to its original position followed by second ‘‘down and up” cycle on the same sample. All operations were automatically controlled and calculated ‘‘Nexygen Lot” software connected to the texture analyzer.

Statistical Analysis

All values given were the mean of three replications and were expressed as the mean ± standard deviation ($\bar{x}$ ± SD). Significant differences between the mean values ($P \leq 0.5$) were determined by using Student test.

RESULTS AND DISCUSSION

Seed properties

The morphological characteristics and physical properties of seeds were presented in Table 2. Significant differences ($P \leq 0.05$) were observed for various physical parameters. The seed weight and volume for Kabuli and Desi chickpea cultivars ranged from 26.73 to 63.10 g/100 seeds and 20.67 to 50.66 ml/100seeds, respectively. The highest seed weight (63.10 g/100seeds) and volume (50.66 ml/100seeds) were observed for Kabuli cultivar. Kaur et al.[7] reported mean of seed weight and volume of 21.94 g/100 seeds and 17 ml/100seeds, respectively for Indian chickpea cultivar (Kabuli type). The differences can either due to intrinsic factors (mainly genetics) or to extrinsic factors such as climatic factors and environmental treatments. The two cultivars have no significant difference in terms of seed density (~1.2). This result is comparable to that of earlier researchers[20] who reported that seed density varies from 1.18 g/ml to 1.65 g/ml for seed cultivar grown in Punjab, Pakistan.

Time (min)	Temperature(C)	Buffer	Ninhydrine	Flow (ml/h)
1	45	Tampon A	+	25
2	45	Tampon A	+	25
8	45	Tampon A	+	25
28	56	Tampon B	+	25
5	65	Tampon C	+	25
25	90	Tampon C	+	25
6	90	Tampon D	+	25
5	90	Tampon A	-	25
2	45		-	25
2	45	Tampon A	-	25
5	45	Tampon A	+	25

Table1: Analysis conditions of amino acids in HPLC.

Parameters	Kabuli cultivar	Desi cultivar
Seed weight (g/100 seeds)	63.10 ± 0.58^a	26.73 ± 0.66^b
Seed volume (ml/100 seeds)	50.66 ± 1.15^a	20.67 ± 1.15^b
Seed density (g/ml)	1.24 ± 0.01^a	1.29 ± 0.05^a
Hydration capacity/seed (g/seed)	0.25 ± 0.01^a	0.64 ± 0.01^b
Hydration index	0.94 ± 0.08^b	1.01 ± 0.02^b
Swelling capacity/seed (ml/seed)	0.29 ± 0.01^a	0.68 ± 0.02^b
Swelling index	1.42 ± 0.13^a	1.34 ± 0.01^a
Cooking time (min)	114.16 ± 5.57^a	64.50 ± 8.3^b

Each value is expressed as mean ± SD (n=3). Means, in the same line, with different letters are significantly different ($p \leq 0.05$).

Table 2: Physical and cooking characteristics of chickpea seeds.

Hydration capacity is related to the presence of soluble molecules like amylose and albumins. Although hydration capacity/seed of Desi (0.64 g/seed) and Kabuli (0.25 g/seed) cultivars varied significantly ($P \leq 0.05$), the hydration index of the two cultivars had no significant difference ($P \leq 0.05$). Desi cultivar showed the highest values of swelling capacity/seed (0.68 ml/seed) and hydration capacity (0.64 g/seed). The higher water absorption of Desi may be attributed to its small size and the greater permeability of its seed coat. Indeed, earlier studies reported that water absorption characteristics of legume seeds is related to the seed size and coat thickness.[7] Swelling capacity/seed and swelling index for different chickpea cultivars ranged between 0.29-0.68 ml/seed and 1.34-1.42 respectively. Singh et al.[20] reported similar values for swelling capacity/seed (0.18-0.20 ml/seed) and swelling index (0.23-1.48) in different chickpea cultivars. Swelling index is related to the gelatinization of starch reflecting the breaking of intra-molecular hydrogen bonds in the crystalline regions and uptake of water by hydrogen bonding; water absorption by non-starch polysaccharides and proteins. The cell structure, composition of seed and compactness of the

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cells in the seed play an important role in the water-absorbing capacity of seeds.[35]

Cooking time is a heritable characteristic that differs widely among genotypes.[7] Chickpea seeds are usually cooked to soften the grain to produce a texture that is acceptable to the consumer and to improve the nutritional quality of the seed.[36] In the present study, cooking time varied significantly ($P \leq 0.05$) and ranged between 64 and 114 min. The longer cooking time for Kabuli cultivar could be attributed to its larger seed weight and size, so the water takes more important time to achieve the core. The difference in cooking times among legumes could be related to the rate at which cell separation occurs due to the loosening of intercellular matrix of the middle lamella upon cooking.[37] Other values reported for cooking time in the literature fall between 62.4 and 95.0 min the lowest value for Desi chickpea type and the highest for Kabuli type.[6]

Flour Properties

Physico-chemical characteristics

***Chemical composition:** The proximate composition of the seed flours from different chickpea were presented in Table 3.

	Kabuli cultivar	Desi cultivar
Dry matter (%)	92.96 ± 0.15^a	92.23 ± 0.92^b
Ash	3.14 ± 0.07^a	3.22 ± 0.06^a
Crude fat	5.20 ± 0.87^a	6.54 ± 0.44^a
Proteins	24.51 ± 0.27^a	20.29 ± 0.13^b
Crude fibers	21.86 ± 0.55^a	18.73 ± 0.52^b
Insoluble fibers	12.50 ± 0.96^a	10.69 ± 0.86^a
Soluble fibers	9.75 ± 0.15^a	8.04 ± 0.34^b
Carbohydrates	70.17 ± 2.86^a	72.88 ± 0.63^a
soluble sugars	1.97 ± 0.07^a	2.44 ± 0.01^b
Polysaccarids	69.18 ± 1.46^a	70.38 ± 0.55^a

Each value is expressed as mean ± SD (n=3). Means, in the same line, with different letters are significantly different *(p≤0.05)*.

Table 3: Chemical composition (g/100g dry weight basis) of chickpea flours.

The moisture content shows significant difference between Kabuli and Desi flours. The ash and crude fat contents of cutivars ranged from 3.14%-3.22% and 5.2%-6.54% respectively. The two cultivars did not present significant differences ($P \leq 0.05$) in terms of ash and crude fat contents. The mean values for ash and crude fat contents of 2.7% and 5.9% have been reported respectively, for Canadian chickpea flours.[38]

The protein content of chickpea cultivars differed significantly ($P \leq 0.05$) between the two cultivars, among which Desi cultivar presents the lowest amount (20.29%). This result is in accordance with that reported by Du et al.[5] (22.37%). Differences in protein contents among chickpea cultivars can be related to the genotypic diversity, varietal characteristics and region of cultivation.

The crude fibers and carbohydrates contents of chickpea varied from to 18.73-21.86% and 70.17-72.88% respectively. Desi cultivar was found to have the lowest fiber content and highest carbohydrates content. The concentration of crude fiber is related to seed coat content. The crude fibers and carbohydrates in the present study are in accordance with those for Indian chickpea cultivars.[7]

***Mineral composition:** Table 4 presents the mineral composition of the chickpea flours which vary from one cultivar to another. Calcium was the abundant element content, ranging from 177.94 mg/100 g in Desi cultivar and 187.25 mg/100 g in Kabuli cultivar, followed by manganese, iron, sodium, zinc, magnesium and copper. Copper was found in lower quantity, ranging from 0.58 to 0.7 mg/100 g. The mean values of calcium, sodium, manganese, magnesium, iron zinc and copper content of 200, 103, 1.7, 4.55, 3.4, 3.6 and 11.5 mg/100 g, respectively, for chickpea seeds were reported.[20] Significant differences were found in sodium and manganese content among the studied cultivars. Thus, the observed variation could be explained by various factors such as variety, soil type and treatment type.

	Kabuli cultivar	Desi cultivar
Calcium	187.25 ± 3.32^a	177.94 ± 3.42^a
Sodium	11.26 ± 1.44^a	7.35 ± 0.65^b
Manganese	115.53 ± 2.61^a	133.63 ± 1.85^b
Magnesium	3.88 ± 0.08^a	3.71 ± 0.5^a
Iron	51.11 ± 3.74^a	48.26 ± 2.47^a
Copper	0.7 ± 0.03^a	0.58 ± 0.11^a
Zinc	4.18 ± 0.23^a	3.32 ± 0.27^a

Each value is expressed as mean ± SD (n=3). Means, in the same line, with different letters are significantly different (*p≤0.05*).

Table 4: Mineral composition (mg/100g dry weight basis) of chickpea flours.

***pH, water activity and soluble solids:** The pH and water activity (a_w) are two parameters that encourage or prevent the growth of microorganisms in foods.[39] The pH value of chickpea flours is ranges from 6.36 to 6.48. pH was near 7.

Water activity, which is an indicator of water availability, was in the range of 0.38 to 0.44. These values were lower than the minimum level at which microorganisms can grow (about 0.61). Chenoll et al.[27] reported that water activity for Spanish chickpea was 0.45. (Table 5)

	Kabuli cultivar	Desi cultivar
pH	6.48 ± 0.03^a	6.36 ± 0,03^b
Water activity	0.38^a	0.44^b
Brix	3.05 ± 0.07^a	2.1±0.14^b

Each value is expressed as mean ± SD (n=3). Means, in the same line, with different letters are significantly different (*p≤0.05*).

Table 5: pH, water activity and soluble solids (Brix) of chickpea flours.

Brix varied significantly ($P \leq 0.05$). It ranged between 2.1 and 3.05. Brix value was found higher for Kabuli cultivar (~3.05). This could be attributed not only to the sugar content but also to the soluble proteins.

***Amino acid composition:** In our study, the amino acid profile

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of chickpea flours was determined, and the results are shown in Table 6. Chickpea flours were found to be rich in Aspatic acid, Glutamic acid, and Arginine, and the total amount of these three amino acids was 34.53 g/100 g of protein for Desi cultivar and 36.85 g/100 g of protein for Kabuli cultivar. This result is substantiated by another study[20] which found that the total amount of these three amino acids was 37.8 g/100 g for Desi chickpea seeds. Glutamic acid presented the largest amount varying from 14.90 to 16.71 g/100 g of protein. Significant differences ($p<0.05$) in leucine, lysine and serine content were observed between the cultivars. The essential amino acids were present in chickpea seeds except Tryptophan and cysteine. The sulphur-containing amino acid content (methionine) was 1.41, 1.14 g/100 g for Desi and Kabuli cultivars, respectively. These amino acids were the first limiting amino acids, which are also in agreement with those found in earlier research works.[20]

Amino acids (g/100g of proteins)	Cultivar	
	Desi	Kabuli
Histidine	3.27±0.05^a	2.70±0.03^b
leucine	4.24±0.04^a	2.48±0.02^b
Lysine	7.25±0.08^a	7.63±0.06^b
Methionine	1.41±0.03^a	1.14±0.01^b
Phenylalanine	5.84±0.02^a	4.53±0.07^b
Threonine	4.02±0.01^a	4.02±0.06^a
Valine	4.69±0.08^a	3.20±0.04^b
Tyrosine	2.87±0.02^a	6.93±0.05^b
Total Essential amino acids	**33.59**	**32.63**
Arginine	8.90±0.05^a	8.84±0.08^a
Alanine	4.11±0.04^a	3.52±0.02^b
Aspartic acid	10.73±0.07^a	11 .30±0.01^b
Glutamic acid	14.90±0.06^a	16.71±0.09^b
Glycine	3.90±0.01^a	3.90±0.02^a
Proline	3.63±0.02^a	2.95±0.01^b
Serine	5.40±0.03^a	7.33±0.03^b
Total Non essential amino acids	**51.57**	**54.55**

Each value is expressed as mean ± SD (n=3). Means, in the same line, with different letters are significantly different ($p\leq0.05$).

Table 6: Amino acid profile of Desi and Kabuli chickpea seeds.

Functional properties: Functional properties play an important role in physical qualities and ingredients of food during preparation, processing and storage.[40]

***Protein solubility:** Protein solubility of the flour was investigated at pH ranging from 2 to 12 (Figures 1A and 1B) to provide information about their use in various food applications.

In general, for the two types of flour, the profile was the same. Protein solubility showed a decreasing solubility with increasing pH until it achieves minimum solubility in the isoelectric point. After this point, solubility increased progressively with the increase in pH values. Studies conducted by other researchers have also shown the same result for other common legumes such as kidney bean[41] and *Mucuna* beans.[42]

The solubility was very low in the range of pH 4-5. The sample had a solubility of 14% for Kabuli cultivar and 17% for Desi cultivar. Vani and Zays[43] reported that isoelectric pH of the most of the plant proteins was about 4-5. At the isoelectric point, there is no charge and no repulsive interactions protein-protein, which result in the unfolding of proteins.

In the neutral pH, proteins solubility is generally higher than 30%. The proteins of the Desi cultivar had the highest solubility in pH=7. Above this pH, protein solubility increased to achieve maximum at pH=12. At this pH, significant differences ($P\leq0.05$) were observed. In fact, solubility was 67.88% for Kabuli proteins and 79.11% for Desi proteins. These differences could be related to the physico-chemical characteristics exhibited by these species, the nature of protein and their behavior in different values of pH.

***Water and oil holding capacities:** Water Holding Capacity (WHC) is of great importance from an industrial point of view.

WHC ranged between 73.89 and 107.96 g/100 g of flours (Figure 2), with the lowest value is for Kabuli cultivar. The two cultivars have significant differences ($P\leq0.05$) in terms of water holding capacity. The varied WHC may be due to the presence of different type of hydrophilic carbohydrates and varied protein structure. These values are lower to than those re-

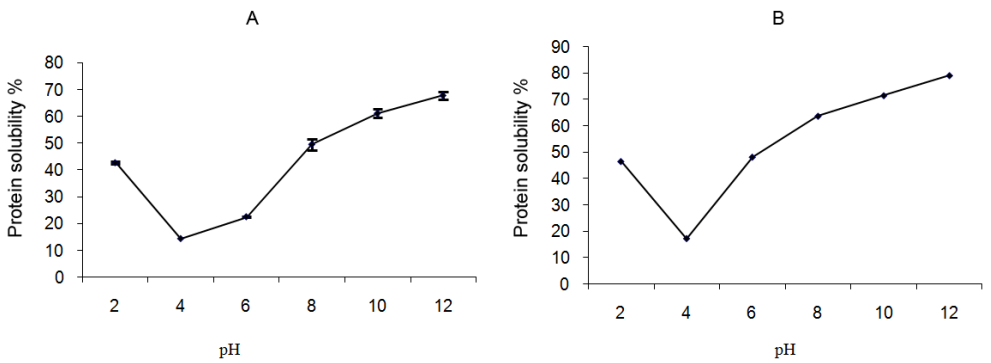

Figure 1: Effect of pH on protein solubility. (A): Desi cultivar, (B): Kabuli cultivar. Values are means of three replications ± SD.

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ported for other flours from Indian chickpea.[30] In addition, WHC of chickpea powders was poor as compared with the values observed in yellow pea seeds flours that generally swell up to 3-4 times their weight.[44] The low WHC could be attributed to the presence of carbohydrates and other components that may not allow the proteins to swell, dissociate and unfold.[45]

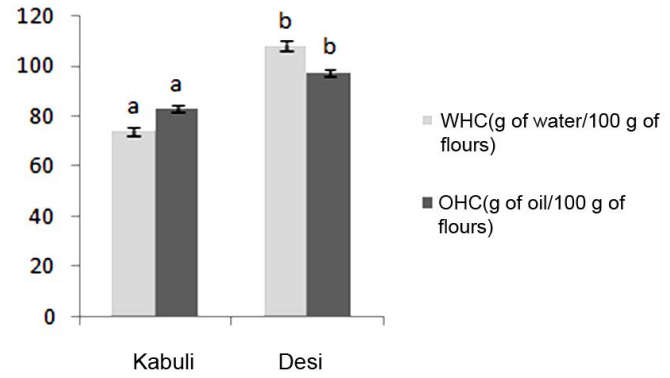

Figure 2: Water Holding Capacity (WHC) and Oil Holding Capacity (OHC) of flours from different chickpea cultivars. Values are means of three replications ± SD. Identical letters above the bars indicate no significant differences by student test ($p \leq 0.05$).

Oil Holding Capacity (OHC) is desired in meat formulations, flavor retention and improvement of palatability. OHC was in the range of 82.88 and 97.40 g/100g of flours (Figure 2). A higher OHC value of 105-124 g/100g has been reported for Indian chickpea in the literature.[30] The difference in oil binding capacity could be related to the presence of non- polar chains, which can form hydrophobic interactions with hydrocarbon chains of lipid.[41] Thanks to its higher fat absorption, Desi chickpea flours may be more appropriate to be used in foods for which fat retention is desirable.

***Foaming properties:** Flours are capable of producing foams due to surface active proteins. The Foaming Capacity (FC) and Foaming Stability (FS) are used as indicator of the whipping properties of protein.[46]

The FC values (percentage of entrapped gaz) of flours from different chickpea were observed in the range of 36.9-41% and found to generally not significant different (Figure 3A). FC of 15-20% for Indian chickpea flours has been reported. Good foamability could be related to flexible protein molecules that can reduce surface tension.

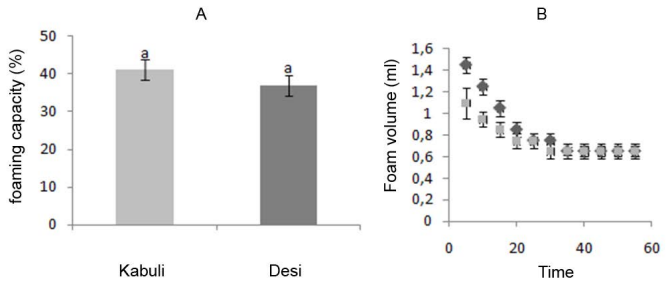

Figure 3: Foaming properties of flours from different chickpea cultivars. (A): Foaming capacity, (B): Foaming stability: ■: Kabuli cultivar, ■: Desi cultivar. Values are means of three replications ± SD. Identical letters above the bars indicate no significant differences by student test ($p \leq 0.05$).

FS is important since the usefulness of whipping agents depends on their ability to maintain the whip as long as possible.[38] The decrease in foam volume as a function of time was observed (Figure 3B) for the two types of flours. A similar trend has been reported for Indian chickpea.[4]

***Emulsifying properties:** The decrease in Emulsifying Activity (EA) was noted with the increase in concentration of flours (Figure 4). No Significant difference ($P \leq 0.05$) was seen in EA between the two cultivars in all concentration. A similar aspect was reported for soybean and sunflower.[34]

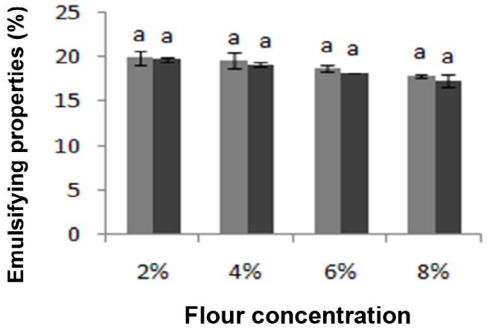

Figure 4: Emulsifying properties of flours from different chickpea cultivars ■: Kabuli cultivar, ■: Desi cultivar. Values are means of three replications ± SD. Identical letters above the bars indicate no significant differences by student test ($p \leq 0.05$).

At low protein concentration, the rate of adsorption is diffusion-controlled, but at a higher protein concentration, there is an activation barrier for adsorption and its rate is mainly determined by the ability of the protein molecule to create space, penetrate and rearrange on the existing film.

***Gelation properties:** The Least Gelling Concentration (LGC) is used as indicator of the gelation capacity concentration to form gels. The LGC is very important in the preparation of many foods products that require thickening and gelling. Table 7 summarizes the gelling properties. In our study, the gelation properties increased with the increase in flours concentration. Gelation was not observed until 12%. This feature may be attributed to the globular nature of protein, which is required in high concentration for gelation. A strong gel was formed at 14% for Kabuli cultivar and 16% for Desi cultivar. The study[30] reported that firm and resistant gel are formed from Indian chickpea flours at 10-14% concentrations. The variation is attributed to the differences in ratio of proteins, lipids and carbohydrates.[40]

The textural measurements of cooked chickpea seeds from different cultivars are presented in Table 8. In fact, hardness which is the maximum height of the force peak on the first compression cycle ranging between 0.69 and 1.68 N and was higher for Kabuli cultivar compared to Desi. This could be attributed to its highest amylose content. Chemical compounds like fiber lignin cellulose and hemicelluloses contribute to the hardness of the gel.[3]

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Concentration	Kabuli cultivar		Desi cultivar	
(% w/v)	Gelation	Appearance	Gelation	Appearance
2	–	Liquid	–	Liquid
4	–	Liquid	–	Liquid
6	–	Liquid	–	Liquid
8	–	Liquid	–	Liquid
10	–	Liquid	–	Liquid
12	±	Viscous	–	Liquid
14	+	Gel	±	Viscous
16	++	Firm gel	+	Gel
18	+++	Firm gel	++	Firm gel
20	+++	Very firm gel	+++	Firm gel

Table 7: Least gelation concentration of chickpea flours after heating in boiling water for 1h followed by cooling for 2h at 4 °C.

Cultivars	Hardness (N)	Cohesiveness	Springiness (mm)	Gumminess (N)	Chewiness (N mm)	Fracturability (N)
Kabuli	1.62±0.18^{a}	0.40±0.02^{a}	10.13±0.26^{a}	0.66±0.04^{a}	6.67±0.23^{a}	1.15±0.16^{a}
Desi	0.69±0.1^{b}	0.63±0.04^{b}	13.74±0.08^{b}	0.43±0.03^{b}	6.04±0.38^{a}	0.51±0.06^{b}

Each value is expressed as mean ± SD (n=3). Means, in the same line, with different letters are significantly different ($p \leq 0.05$).
Table 8: Texture parameter of chickpea flours.

Significant differences were observed among cultivars such as cohesiveness (ratio of the positive force areas under the first and second compressions), gumminess (product of hardness and cohesiveness) and springiness (height to which the sample recovers during the time elapse between the end of the first compression and the start of second compression). Desi cultivar had the highest cohesiveness (0.63 *vs.* 0.40) and springiness (13.74 mm *vs.* 10.13 mm) and lowest gumminess (0.43 N *vs.* 0.66 N). Fracturability, which is defined as the force of the significant break in the curve on the first bite, ranged between 0.51 and 1.15 N for Kabuli and Desi cultivar. These differences on textural parameters could be attributed to the chemical differences (protein and starch content).

CONCLUSION

The chemical composition of flours has shown that chickpea is an available source of proteins and fibers. Wide variations in physico-chemical, cooking and functional parameters of different chickpea cultivars were observed. In fact, Desi chickpea cultivars with low seed weight had lower cooking time and higher water absorption. Protein solubility is pH-dependent (minimum at pH) and higher at alkaline pH. Gelation and emulsifying properties are influenced by flours concentration. Considering flours contents and functional properties of chickpea seeds, we conclude that they could be useful in flavor retention, improvement of palatability and extension of many products.

This study will promote the culture of chickpea for the local consumption and fractionation of this agro-resource for the production of local food ingredients as proteins. Future work will focus on the optimization of the extraction of the protein concentrates of chickpea and the characterization of their functional properties according to the experimental conditions and to the drying methods.

CONFLICTS OF INTEREST: None.

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Systematic Review

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Green Tea Catechins as Neuroprotective Agents: Systematic Review of the Literature in Animal Pre-Clinical Trials

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ABSTRACT

Alzheimer's Disease (AD) is a neurodegenerative disorder and the most common form of dementia, with symptoms and manifestations that progressively get worse with increasing age. Therefore, with the ageing of the population worldwide, the prevalence of AD is increasing. There is no current cure for AD and, as a result, there has been a recent rise in interest in plant bioactive compounds that may prevent or improve symptoms of the disease. Currently, the nootropic potential of plant derived compounds that can combat damage posed by free radicals is being investigated. Antioxidants, in particular, the Green Tea Catechins (GTC), have been shown significant interest due to their exceptionally strong antioxidant and anti-inflammatory properties. The aim of this paper was to perform a systematic review based on the PRISMA guidelines in order to evaluate the effectiveness of GTC as a potential treatment to suppress or delay the onset of AD in pre-clinical animal trials. The paper reports on three animal pre-clinical trials in which rat or mice models of AD were used to test the effects of GTC or the pure form of the predominant GTC, Epigallocatechin gallate (EGCG), administered orally or by injection. The reviewed papers show that GTC extracts or pure EGCG had preventative effects on AD in the various animal models used, including the enhancement of learning and memory, possibly through the reduction in oxidative stress, β-amyloid plaque build up and Tau protein phosphorylation. Therefore, GTC extracts or EGCG in its pure form may serve as nootropic options in the prevention or treatment of neurodegeneration-associated diseases such as AD.

KEYWORDS: Green Tea Catechins; EGCG; Oxidative stress; Neuroprotection; Pre-clinical animal trials; Alzheimer's disease; Beta amyloids; Tau protein.

ABBREVIATIONS: AD: Alzheimer's Disease; GTC: Green Tea Catechins; LPO: Lipid peroxides; ROS: Reactive Oxygen Species; EGCG: Epigallocatechin gallate; MPTP: N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; EGC: Epigallocatechin; ECG: Epicatechin gallate; TBARS: Thiobarbituric acid-reactive substances; SOD: Superoxide dismutase; IP: Intraperitoneal; RAWM: Radial Arm Water Maze; FRAP: Ferric Reducing Ability of Plasma; APP: Amyloid Precursor Protein.

INTRODUCTION

Mental disease represents one of the world's leading disabilities affecting over 25% of people at some period during their lifetime. In 2004, it represented 13% of the global burden of disease and it is proposed to increase to 15% by the year 2020, which will place it as the second leading cause of disability in the world.[1,2] Alzheimer's Disease (AD) and cognitive im-

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pairment are on the increase and have been identified as contributing to the overall increase in mental disease, which indicates an increasing prevalence of disorders of later life rather than of childhood.[3-5] The increasing incidence of these types of mental disease can also be viewed as being due to the rapid ageing of the world's population and the fall in the birth rate, which has resulted in an overall lower prevalence of the types of mental disease associated predominately with adolescence.[6]

Much of the scientific research in the elderly has been devoted to studies on the implications of the cognitive decline and impairment that characterise the dementive-type illnesses. Dementia is a disease of the brain, and the term "dementia" is classified as an "umbrella" term for various types of diseases. These are characterised by the development of multiple cognitive impairments that can arise due to different causes such as direct physiological effects of a medical condition, persisting effects of substance abuse or multiple other aetiologies. Therefore, there are various types of dementia such as dementia of the Alzheimer's type, vascular dementia and dementia due to various diseases such as HIV and Parkinson's disease.[7,8] It is also important to note that the aetiology of certain types of multiple cognitive deficits cannot be identified and thus, "Dementia Not Otherwise Specified" is another type of this disease.[7]

Studies have identified dementia of the Alzheimer's type to be the most prevalent form of dementia.[9,10] The AD dementia has therefore become the most well-known type of dementia chiefly associated with older age.[7,11,12]

The onset of AD is categorised by two subtypes according to age: early onset AD where symptoms of this type of dementia manifest themselves before 65 years of age and late onset AD with symptoms emerging after the age of 65.[7] The use of 65 as the age cut-off point is completely arbitrary from a health point of view as it does not have any medical significance.[13] Obviously however, it is related to the age that is normally associated with retirement from work.

The behavioural and cognitive onset of AD can be slow and gradual; it predominately manifests itself as a slow but progressive cognitive decline.[7] Furthermore, there is no one universally accepted neuropathologic criteria to differentiate AD from healthy brain ageing primarily because AD is a complex neurodegenerative dementing illness.[14-16] However, the fundamental neuropathologic features of AD, based on the post-mortem examination of patients' brains, include reduced brain volume, enlarged ventricular spaces, region specific neurofibrillary tangles and neuritic amyloid plaques.[17,18] The exact causative factor for these brain changes still remains unknown. However, the final resulting physiological outcome is death of neural cells which causes severe cognitive impairment and eventually death of the patient suffering from AD.[11,13,15,16]

It has been proposed that death of the neural cells is a result of a cascade of intracellular and extracellular events.[16,17] There are several different factors which have been postulated to directly or indirectly play important roles in the initiation of these events: oxidative damage,[19,20] genetic polymorphisms,[21,22] gene mutations[23] and abnormal levels of β-amyloid and tau proteins.[24] Of these, the deposition of β-amyloid protein is seen as the primary event in the pathogenesis of AD. The other changes such as neurofibrillary tangles, synaptic degeneration and neuronal cell death are proposed to arise only as a consequence of the deposition of this protein in the brain.[25]

In addition, neurodegeneration is a common feature of AD with the main reasons described to be the combination of multi-factorial events such as neuro-inflammation, glutamate rich excitotoxicity and depletion of antioxidants.[26] Hence, in recent years there has been developing evidence proposing that dietary polyphenols can potentially counteract and suppress the neuronal injury.[26-29]

Polyphenols are ubiquitous compounds classified as wide and complex group of plant secondary metabolites and to date there have been over 8000 compounds identified. Additionally, these compounds are exceptionally diverse in their structures, ranging from very simple molecules (phenolic acids) to more complex and highly polymerized structures (proanthocyanidins).[30-36] The polyphenols are generally divided into two groups based on their molecular weight, low (500-3000 Da) and high molecular weight (>3000 Da).[37] In addition, these compounds can also be classified into different groups based on the number of phenolic rings that they contain and on the basis of the structural elements by which these rings are connected to one another. They include such compounds as phenolic acids, flavonoids, stilbenes and lignans (Figure 1).

One of the foods rich in bioactive compounds, particularly flavonoids, is green tea (*Camellia sinensis*). In recent years, there has been a significant upward trend in the consumption of green tea and taking into consideration that overall tea (black and green) is one of the most consumed beverages in the world, it is not surprising that this trend was closely followed by academic research interest.

The most abundant polyphenolic compounds in green tea are the catechins, which account for nearly 30% of the dry tea leaf weight.[38] In the recent literature, the Green Tea Catechins (GTC) have been related to a variety of different beneficial health effects particularly with respect to their potential for preventing and treating different cancers,[39,40] cardiovascular diseases,[41-43] inflammatory diseases[44-47] and some of the neurodegenerative diseases[45,48,49] in humans. Accounting for at least half of the total GTC,[38] the most predominant catechin found in green tea is Epigallocatechin gallate (EGCG), which has been ascribed numerous beneficial properties including antioxidant,[50] anti-inflammatory,[51,52] anti-microbial[53,54] and anticancer effects.[55-57]

Although current trend in the scientific writing of systematic reviews is chiefly reserved for trials with human subjects

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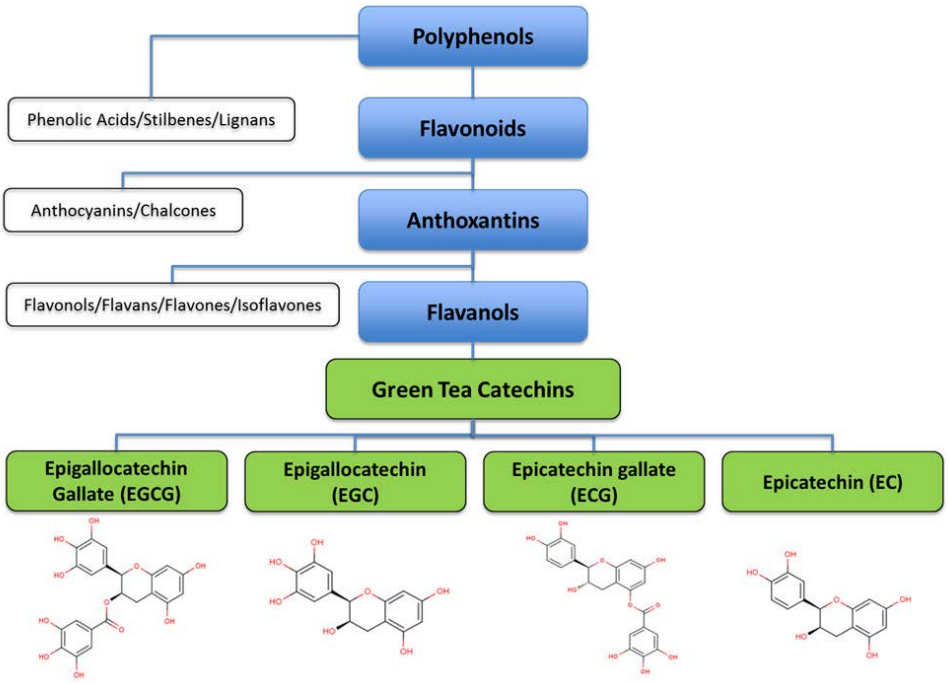

Figure 1: Brief representation of the polyphenols classification with focus on green tea catechins.

from various cohorts, the use of well-designed pre-clinical animal trials is gaining value. This is primarily due to the increased number of well-developed gene-knockout animal models that can be used to mimic certain diseases commonly occurring in humans. Additionally, some of the illnesses such as AD can only be successfully diagnosed post-mortem. Therefore, keeping in mind that findings from animal models are not necessarily directly transferrable to humans, these studies still provide valuable insight into the potential mechanisms of action that may be applied to clinical research in humans. Therefore, the aim of this systematic review is to look into what is known about the relationship between GTC and the leading biomarkers associated with the development of AD.

METHODS

Animals

The animals used as models in the pre-clinical animal studies covered in this systematic review were rodents in particular rats (JCL: Wistar) and mice (C57/BL; Tg2576; APPsw; non-transgenic).

Search Strategy

The standardized criteria for conducting and reporting systematic reviews of observational studies based on the PRISMA 2009 guidelines[58] were used. The search strategies were applied for articles published since the year 2000 using the following electronic databases: PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), the Cochrane Library (http://www.thecochranelibrary.com/view/0/index.html), and Scopus (http://www.elsevier.com/online-tools/scopus). Titles and abstracts were scanned for relevance and appropriate articles were selected.

The search used terms relating to the topic of this systematic review; "*Green tea polyphenols*" and "*Alzheimer's Disease*" were used in the primary search followed by "*Beta Amyloid*", "*Neuroprotection*" and "*Catechins*" in the secondary search. In addition, reference list checks of selected articles with relevance to the topic were also performed.

Selection Criteria

For the purpose of this systematic review, articles were selected only if they were entirely published in English, in peer-reviewed journals and were identified as pre-clinical animal trials. They were included if GTC were delivered as a part of a supplement, injection, oral consumption in tea, water, food or similar delivery methods. Furthermore, studies selected for review had sample sizes of over 5 animals (at the end of the study) of any gender and had identified looking at whether or not GTC affected one or all of the biomarkers in relation to the development and onset of AD.

Primary Outcomes

The primary outcomes were cognitive learning and abnormal levels of β-amyloid and tau proteins in brain homogenates.

Secondary Outcomes

The secondary outcomes were oxidative stress identification by the presence of Lipid peroxide (LPO) by-products and generation of Reactive Oxygen Species (ROS).

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Materials

Studies used green tea extracts, GTC or pure EGCG in the intervention and the control groups were always administered with water containing no additional compounds or in a case of injections, animals were injected Intraperitonealy (IP) with sterile saline or not injected at all.

RESULTS

Characteristics of the Studies

Preliminary searches of the selected databases identified 4635 records with the terms "*Green tea polyphenols*" and "*Alzheimer's disease*" alone (Figure 2) but the secondary search reduced this to 500 articles. These 500 abstracts were screened, of which only 3 studies (1 in rats and 2 in mice) were included in the review because they fitted all the eligibility criteria.[59-61] These 3 articles were published after the year 2000; included animals in the pre-clinical setting treated orally or injected with a GTC supplement or an individual purified catechin and also included control groups.

GTC or EGCG Supplementation Doses

The 3 articles included in this review utilized either a GTC preparation or pure EGCG as the treatment method in animals. In the study with rats,[59] the animals were orally treated with an aqueous GTC extract, referred to as Polyphenon E (Mitsui Norin CO. Ltd, Tokyo, Japan), which had an initial concentration of total catechins of 0.5% (w/v). The extract was diluted daily in the animals' drinking water to provide the following concentrations of the individual catechins: EGCG (63%); EC (11%); EGC (6%) and ECG (6%). The control group received drinking water with no catechins in it.

One of the 2 studies in mice[60] also used a GTC powdered extract (Plant extract GmbH & Co, KG, Vestenbergsgreuth, Germany) in which the catechin concentration was said to vary between 12 and 17% (w/w). In this study, some mice were IP injected with 0.5, 1 or 5 mg/kg of the GTC extract in saline (twice on the first day of the experiment with a 6 hr interval) followed by once for the next 4 days. Control mice were injected with saline. In the same paper, other mice received oral treatment with pure EGCG at two concentration levels (2 and 10 mg/kg/day) for 14 days.

In the other mice study,[61] some of the animals (Tg2576 females) were orally administered with pure EGCG (50 mg/kg) in water or water only (control) on a daily basis for 6 months. Other mice (female APPsw) were treated by IP administration of EGCG (20 mg/kg) or vehicle only (control) daily for 60 days.

Cognitive Testing

Rats were tested for learning-related cognitive ability with the use of the eight-arm radial maze with a particular focus on the reference memory error and working memory error.[59] The

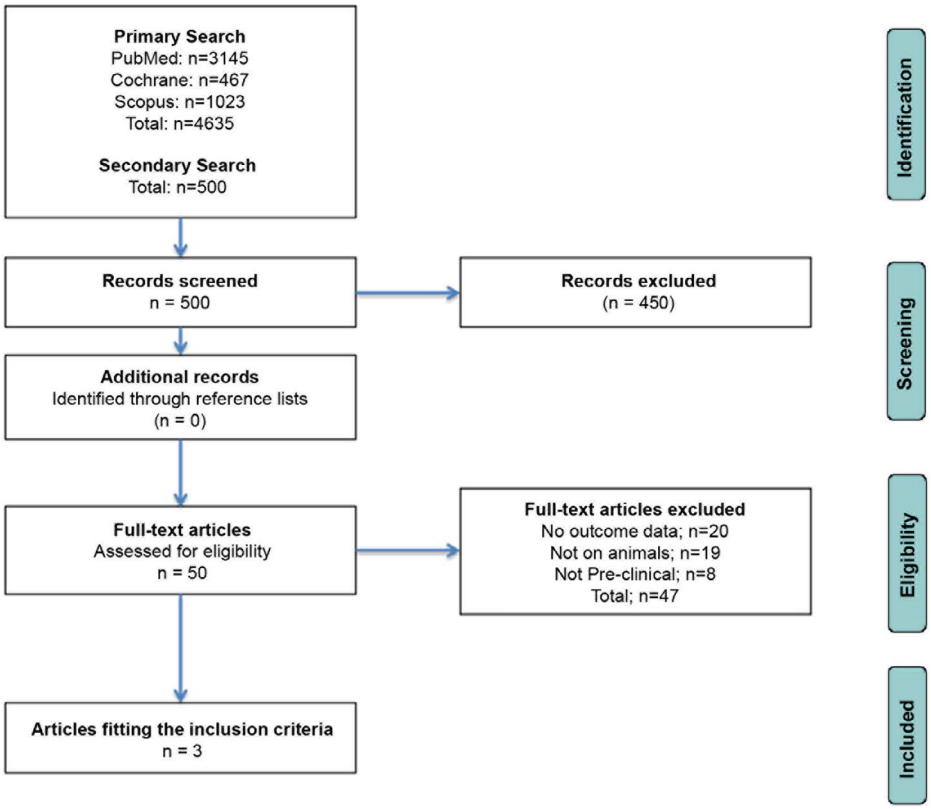

Figure 2: Flow chart of the publication selection process.

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Radial Arm Water Maze (RAWM) was also used to assess the experimental mice for working memory.[61]

Induction of Cognitive Deficits/Mimicking of Ad Symptoms in Animals

One of the mice studies included "*Swedish*" mutant amyloid precursor protein overexpressing (APPsw, Tg) mice,[61] while the other study injected the mice IP with N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) at levels of 24 mg/kg/day in order to replicate the clinical AD symptoms.[60] However, in the Wistar rat study, the animals were infused with A$\beta_{1\text{-}40}$ (4.9-5.5 mmol/l) into the exposed left ventricle after the injection of $AlCl_3$ (0.5 µg) was performed in the right ventricle.[59]

Tissue Analysis/Testing

In the mice studies, the brain homogenate tissues were analyzed using Western blots and immunohistochemistry techniques with a specific focus on soluble A$\beta_{1\text{-}40}$[61] and tyrosine hydroxylase.[60] In the rat study,[59] plasma and brain homogenates were tested for LPO concentrations using the Thiobarbituric acid-reactive substances (TBARS) assay while plasma was also analyzed for total antioxidant activity using the Ferric Reducing Ability of Plasma (FRAP) assay and for plasma triglycerides and total cholesterol using commercially available enzyme kits.

Study Outcomes

One of the studies by Rezai-Zadeh, et al.[61] was done to determine if the oral administration of ECGC would cause a reduction in plaque build-up in the APPsw mice. It was found that the ECGC (50 mg/kg) treated mice had significantly reduced ($p<0.05$) plaque build-up compared to controls (Table 1). This was supported by the micrographs of the brain sections where it was identified that β-amyloid stained antibody sections were substantially reduced in the cingulate and entorhinal cortex, as well as in the hippocampus by 54%, 51% and 43%, respectively. This was further supported by analysis of the anterior quarter brain homogenates, which indicated that the oral consumption of EGCG significantly ($p<0.05$) decreased both the soluble and insoluble forms of β-amyloid plaques.[61] In addition, the Tau protein formation induced by the deposition of β-amyloid plaques was also suppressed in the EGCG treated mice.

The second study by Rezai-Zadeh, et al.[61] was done to examine whether EGCG had potential cognitive benefits, either by IP injection or by oral intake (Table 1). The results identified that the animals, after two months of IP injections with EGCG, had an improved working memory compared to the controls ($p<0.001$). This was supported during the final stage of the RAWM testing where the EGCG treated transgenic animals showed improvements between the trials while the control non-transgenic mice showed no working memory improvements. A similar finding was also identified for animals that consumed the EGCG orally (50 mg/kg); the transgenic mice were not weakened in working memory compared to the non-transgenic control animals.

The study by Haque, et al.[59] in JCL: Wistar rats was focused on the effects of GTC on three measures: AD precursors/indicators, plasma and brain tissue (hippocampal and cerebral cortex) oxidative stress and outcomes of the eight arm radial maze test (working and reference memory errors) (Table 1). The plasma TBARS concentrations were significantly ($p=0.02$) higher in the control rats infused with the vehicle only and in rats infused with A$\beta_{1\text{-}40}$, whether they were pre-administered with Polyphenon E or not, compared to the animals infused with Polyphenon E only. However, the plasma FRAP was significantly ($p<0.0001$) higher in the Polyphenon E pre-administered groups, compared to controls, whether they were infused with A$\beta_{1\text{-}40}$ or not. Furthermore, the plasma cholesterol levels were significantly ($p<0.05$) lower in the polyphenon E treated A$\beta_{1\text{-}40}$ infused group compared to the rest of the experimental groups although the plasma triglycerides were not significantly ($p>0.05$) different amongst the groups.

The hippocampal TBARS concentrations were significantly ($p<0.0001$) lower as were the ROS levels ($p=0.0029$) in the A$\beta_{1\text{-}40}$ infused rats pre-administered with Polyphenon E. The cerebral cortex TBARS concentrations were unaffected ($p=0.2$) amongst the groups but the Polyphenon E only group (no A$\beta_{1\text{-}40}$ infused) had significantly ($p<0.05$) lower concentrations of ROS compared to the other groups.

The subset analysis of the number of radial maze error scores also indicated that Polyphenon E has significant effects in both the vehicle only and A$\beta_{1\text{-}40}$ infused rats. The Polyphenon E pre-treated groups had significantly ($p<0.0001$) lower error scores than either the A$\beta_{1\text{-}40}$ infused or vehicle treated animals.

The study by Levites, et al.[60] investigated the neuroprotective properties of a GTC extract and pure EGCG in the MPTP mice model of dopaminergic neurodegeneration similar to that found in sufferers of Parkinson's disease (Table 1). In this study, it was identified that pre-treatment of the mice with either GTC at two doses (0.5 and 1 mg/kg) or with pure EGCG at two doses (2 and 10 mg/kg) prevented the neuronal losses caused by the MPTP treatment and concomitantly prevented the depletion of dopamine and tyrosine hydroxylase in the substantia nigra of the mice's brains. It was identified that the GTC extract provided significant protection against the MPTP induced decrease in the melanin containing dopamine neurons at the GTC doses of 0.5 and 1 mg/kg although the higher dose of 5 mg/kg GTC was not effective. In addition, the pure EGCG at 2 and 10 mg/kg also considerably prevented the decrease in striatal dopamine neurons induced by the MPTP.

Furthermore, the activities of the SOD and catalase enzymes were assessed in the striatum of the mice treated with EGCG, MPTP or both of these compounds. It was observed that the MPTP increased the activity of both of these enzymes while

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Author (Year)	Animals, sample size, age	Aim	Intervention	Results
Rezai-Zadeh, et al. (2008)	Female "Swedish" mutant amyloid precursor protein overexpressing (APPsw) (All n=10; C:n=5; T:n=5) Female Tg2576 (All n=10; C:n=5; T:n=5) Female Non-transgenic mice (n=5) Age at start: 8 mth.	Anti-amyloidgenic effects of orally administered EGCG in APPsw mice.	Oral EGCG (50mg/kg) or control (water) treated for 6 mth.	Treatment resulted in a significant reduction in plaque buildup ($p>0.05$) Treatment decreased soluble and insoluble forms of $A\beta_{1\text{-}40,42}$, increased ADAM10 maturation and increased sAAP-α release ($p<0.001$) Provision of comparable attenuation of amyloid pathology to that of IP injections.
		Effect of IP injection EGCG treatment on Tau protein physiology in APPsw mice	Treated 2 months with IP injection of pure EGCG (20mg/kg) or orally consumed EGCG (50mg/kg). Control group did not receive any treatment.	Both treatments (oral and IP injection) decreased Tau hyperphosphorylation ($p<0.001$)
		Cognitive benefits after oral administration of EGCG in APPsw mice		Animals provided with EGCG treatment had substantially improved working memory performance, comparable to non-transgenic non-treated mice ($p<0.001$).
Haque, et al. (2008)	Male JCL:Wistar rats (All=49; C:n=25; T:n=24) Age at start: 5 wk.	Long-term administration of GTC and effect on oxidative stress and cognitive impairment in $A\beta_{1\text{-}40}$ infused AD rat model.	Treatment group was administered GTC combination [EGCG (63%), EC (11%), EGC (6%) and ECG (6%)] in water for 26 wk.	Treatment prevented β-amyloid associated impairment in cognitive learning ($p<0.0001$). Treated rats showed significant decreased number of reference and working memory errors ($p<0.05$). Treated rats also had lower LPO (TBARS) in hippocampus and plasma and ROS in hippocampus and cortex and higher FRAP in plasma.
Levites, et al. (2001)	Male C57/BL mice (All; n=144)	The effects of GTC extract in MPTP injected animals	Mice were IP injected twice on the first day with GTC extract (0.5mg/kg), followed by injection of MPTP (24mg/kg) and GTC extract (0.5mg/kg) for the subsequent four days. For EGCG studies, mice were orally administered EGCG (2 or 10mg/kg/day) for 10 days and then EGCG (2 or 10mg/kg/day) and MPTP (24mg/kg/day) for the following 4 days. Control mice received only saline or GTC extract	The injected GTC extract and oral EGCG showed a protective effect against MPTP-induced decreases in dopamine and tyrosine hydroxylase protein levels ($p<0.05$).
		The effect of EGCG on MPTP-induced neuro-degeneration		The injected GTC extract also prevented the MPTP-induced decrease in dopamine neurons in the brains. ($p<0.02$).
		The prevention of the MPTP-induced increase in the antioxidant enzymes SOD and Catalase by EGCG.		Oral EGCG at 2mg/kg/day, but not at 10mg/kg/day, prevented the MPTP-induced increase in SOD and Catalase.

Table 1: Summary of GTC effects in animal pre-clinical trials.

pre-treatment with EGCG prevented these effects at 2 mg/kg but not at 10 mg/kg.

DISCUSSION

The recent advances in drug development as well as more identifiable characteristics of neurodegeneration have set a path for the utilization of drugs that exhibit free radical scavenging and iron-chelating properties. These compounds can consequently serve as potential treatment of neurodegeneration and act as vehicle mediated "backbones" for human trials on suppressing the development of AD and Parkinson's disease alike. The utilization of pure EGCG and more complex GTC mixtures in the prevention of neurodegeneration has been associated with the catechol-like structures as it is well established that catechol-containing structures are potential antioxidants and free-radical scavengers.[62,63]

The studies outlined in this review have exemplified some of the putative neuroprotective properties that GTC extracts and pure EGCG have on the suppression of neurodegeneration and the preservation of learning and behavioral patterns commonly affected by AD. The studies reviewed identified the benefits of GTC on either the suppression of development or the maintenance of symptoms associated with AD.

The study by Rezai-Zadeh, et al.[61] identified that the oral administration of EGCG diminished amyloidosis in an AD-induced animal model, which is readily identified as one of the hallmarks in the development of AD; EGCG reduced the formation of β-amyloid plaque in the primary neuronal cells.[61,64] Previous studies have predicted and observed that EGCG promotes the cleavage of Amyloid Precursor Protein (APP) into soluble-APP associated with an elevation of α-secretase cleavage, the main pathway for APP processing.[65] Therefore, the findings by Rezai-Zadeh and colleagues[61] indicate that EGCG may potentially reduce the formation of the toxic sarkosyl soluble phospho-tau isoforms that are considered to be one of the features of

AD.[64] In this mouse study, both delivery methods of IP injection and oral consumption of EGCG also independently promoted benefits for cognition and learning by reducing the number of maze errors in the AD-induced animal model.[61]

Furthermore, in the same article,[61] pure EGCG administration to amyloid precursor protein overexpressing (APPsw, Tg) transgenic mice, successfully reduced the development of the neuro-toxic portion of the Tau protein strands.[66,67] The oral administration of EGCG for a six-month period to the AD transgenic mice also reduced β-amyloid deposition and its build up in important cognitive areas of the brain, improving working memory to near perfect results. Therefore, the findings of this study also supported the potential of EGCG to provide cognitive benefits in the transgenic mice models of AD as measured by RAWMS. Finally, these findings strengthen the possibility that the consumption of EGCG can be seen as a feasible therapeutic approach against AD and other similar cognitive impairments, which result from neuro-degeneration.

The study by Haque, et al.[59] demonstrated that the long term pre-administration of PolyphenonE could prevent the development of β-amyloid-induced spatial cognitive learning difficulties in an AD rat model. In this model, the infusion of $A\beta_{1\text{-}40}$ into the rat's hippocampus induced a deficit in long-term potentiation and also in working memory. The β-amyloid infusion also increased hippocampal ROS concentrations, suggesting that ROS generation may lead to impaired learning cognitive functions.

The findings indicated that the neuroprotection and prevention of cognitive learning impairments seen with the GTC extract may have been due to its ability to decrease the β-amyloid induced oxidative stress.[59] The pre-administration of PolyphenonE decreased the LPO (TBARS) and ROS concentrations, induced by β-amyloid infusion, in both the brain and plasma of the rats; the Polyphenon E also increased the FRAP in plasma. These results suggested that there was a significant and independent antioxidant effect of the GTC extract, which could potentially be harnessed to prevent cognitive damage in AD. This increase in antioxidant activity was proposed by the authors to be the main enhancing influence on the memory-related learning observed.[59] These findings were also consistent with other observations that the oral consumption of GTC and other antioxidants is associated with the activation of antioxidative enzymes in various mouse models.[68-70]

In one part of the study in mice by Levites, et al.[60] they utilized MPTP as an initiator of neuro-degeneration caused by depletion of dopamine and tyrosine hydroxylase and showed that a GTC extract could prevent the MPTP-induced decreases in dopamine and tyrosine hydrolase. In a further study using a mice model of cerebral ischemia, pure EGCG injected immediately after ischemia, resulted in less memory impairment and reduced hippocampal neuron damage. Levites Y, et al.[60] suggested that the EGCG's neuroprotective properties may also include the regulation of antioxidant enzymes.

In conclusion, the papers reviewed in this systematic-review indicate that GTC and/or pure EGCG possess neuroprotective properties, which may be useful for preventing the development, or for the maintenance, of AD. Each of the papers reviewed also show effects on one or more of the current biomarkers linked to the development of AD. Although the findings of these articles are associated with pre-clinical animal models, they never the less provide a "stepping stone" for the utilization of GTC or EGCG as nootropic nutraceuticals for the potential suppression of neurodegenerative diseases such as AD.

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Opinion

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Food Questionnaires and Dietary Recalls: The Challenges of Assessing Food Consumption to Identify Poor Nutrition in a Changing World

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Assessing food consumption is challenging. Often, researchers speculate as to what is the best way to gather information about people's food intake. There are many factors intertwined regarding food consumption some of which include: low or high income, nutrition knowledge, food availability and access to food.[1]

Diet has changed in the last decades, emerging as a nutrition transition process which is consequence of two historic processes of change, clearly explained by Popkin et al.[2] the demographic transition – the shift from a pattern of high fertility to one of low fertility and mortality and the migratory movements from rural to urban settings, and the epidemiologic transition process, meaning the change from a pattern of high prevalence of infectious diseases, associated to under nutrition and poor environmental sanitation, to one of high prevalence of chronic diseases associated to urban lifestyles.[2] These changes resulted in changes in physical activity and diet patterns, and one of the most relevant changes within the diet is the poor consumption of fruits and vegetables.[3]

Fruit and vegetables consumption has been reported to be an important factor for the prevention of chronic diseases related to nutrition,[4] in consequence there is much epidemiologic interest for obtaining accurate estimates of mean or median intakes and (when possible) distribution of consumption of these foods.[5] When a particular dietary pattern lacks these foods because they are expensive, and are difficult to access for the poorest segments of population, or because nutrition knowledge is low,[6] it is important to introduce some actions to improve this situation.

In order to examine the dietary intake of the population adequacy, it is important to have validated tools particularly for assessing the consumption of foods that play key roles for preventing diseases in the long term.[7] It is known that many nutrients such as vitamins and minerals are present in fruits and vegetables, giving these foods relevance to maintaining a healthy status for individuals. This fact highlights the significance of assessing the intake of such foods.[8]

The review of the dietary pattern and the detailed analysis of other nutrient consumption of populations are very important to approach the study of the relationship between nutrition and disease.[9] Dietary pattern analysis is, according to some authors a better way to examine the effect of overall diet on diseases related to nutrition, and might well give some insight about the consumption of groups of food.[9] When addressing intake details, other methodologies are to be used.

Differences between methodologies to assess food intake exist, while Food Frequency Questionnaires (FFQ) are designed to assess usual intakes, 24-four hour dietary recalls, on the other hand, can give more accurate nutrition information concerning the previous day recall, it is more expensive to administer and require a high level of cooperation and literacy.[10]

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Whether traditional tools such FFQ or 24 hour recall are used, health care practitioners, epidemiologists and ultimately policy makers, should realize that there may be errors due to memory lapses of participants, misinterpretation by interviewers, poor nutrition education knowledge and the lack of interest by participants in responding to long questionnaires.[11] Still, researchers desire to assess appropriately these populations and each individual's food intake patterns in order to improve overall nutrition (Table 1), overcome nutritional deficiencies and control the chronic non communicable diseases which are epidemic around the world.[12]

The gold standard for assessing food and beverage intake in humans has been the 24 hour recall, however this method not always fits into a nutrition study project, because it requires training, it is time consuming, its analysis is laborious and depending on the circumstances can be expensive. On the other hand, to leave out this tool can be risky if individual needs are to be considered.[11]

In general, identifying population's needs has been challenging since many times food consumption assessment is skipped due to lack of time for engaging in the long and complicated process of questionnaires and recalls, particularly for policy makers that usually request fast results and need short term impact.

The initiative for developing shorter tools to identify specific food and nutrition data, have been taken in the last decades by several institutions over the world including the 5 a Day for Better Health Program,[8] that requires efficient tools to be used to track changes in fruit and vegetables intakes.

As time has progressed, the evaluation of food consumption, coupled with nutritional interventions developed to eradicate existing nutrient deficiencies, has been fraught with difficulty. Even workers on tried intervention programs concur that what is being done is enough, as anything else tried in comparison has complications.[16] Therefore, analyzing in detail the impact of an intervention, an education program or a policy, or what to ask or how to ask, and how much to ask, all becomes relevant.

As expressed by Popkin et al.[2] and Drenowky et al.[14] changing eating patterns are important to identify, as large shifts have occurred toward diets high in saturated fat, sugar and refined foods but low in fiber, vitamins and minerals, many of which are present in fruit and vegetables.[2,17] In consequence, ensuring that the population is consuming enough fresh produce becomes relevant, thus catalyzing fruits and vegetables for the many health benefits of individuals such as preventing inflammation, obesity and type 2 diabetes.[4,18]

Ultimately, one can observe that nutrition risk screening tools are not routinely implemented in many environments. Communities without food consumption surveys, malnourished hospitalized children and adults and countries without nationally representative nutrition studies still exist. The benefit of tools largely proven to be accurate, short, easy to perform and less expensive, are to be included so nutritional and food consumption data can be available, and might give at least a more accurate idea of the real food and nutrient needs of the population.[19] A recent study conducted in pediatric hospitalized patients shows the relevance to implement screening tools for recognizing malnutrition, and the use of a Single Question (SQ), performed adequately to identify nutrition risk on these patients.[19]

In a similar manner, single questions and short questionnaires have been developed for appropriate screening of fruits and vegetables, due to the relevance of these foods for the health of populations. Comparison and validation of short tools such as the one conducted by Cook et al.[20] supports its use to establish population needs. The fact Cook et al. found that using a SQ for assessing fruit consumption, a SQ for vegetable consumption and a 5 item Vegetable Fruit Questionnaire (VFQ) could replace a longer FFQ for estimation of population intakes of these foods and for screening its adequacy is an interesting finding, and is valuable and give some alternatives to the tradi-

24 hour dietary recall	Food Frequency Questionnaire (FFQ)
Take large amounts of time to apply[11]	Less time consuming[11]
Gives information about the food intake of the previous 24 hours[13]	Can be for specific foods such as identifying beverage or fruit intake[20,21]
Better for assessing individual intake at defined periods[13]	Better for assessing usual intake[10]
Limited use in large prospective studies[13]	Better for using in large prospective studies[13]
Require special training for interviewing[11]	Better tool to be self-administered[11]
Under and over reporting of some foods[14]	Can give higher estimates of the intake of some foods particularly of those socially acceptable foods[11]
It is suggested that two 24 h recalls are made and the 5 pass method is the result of reducing the underreporting bias[15]	Depends of how many food items are being questioned and how are the frequency required[10]

Table 1: Comparison between 24 hour dietary recall and Food Frequency Questionnaire.

tional, more complex tools.

The use of a short question to be answered can be a useful tool to identify whether a certain food is being consumed by a population at risk, and give a closer idea of a particular group of food intake that should be promoted, such as a type of milk or fruit.[21]

When conducting studies that aim to identify the extent to which a population is deficient in nutrients mainly found in fruit and veggies, such as antioxidants, these shorter tools can be of much aid in attaining results in a faster way, thus allowing the taking of public actions in a reasonable time. Also, when weighing the pros and cons of conducting nutrition surveys and exploring methodologies it is important to suggest the use of short, evidence based tools that proved efficient and safe for identifying populations at risk.

In populations of the world that are undergoing the nutritional and epidemiologic transition to more caloric diets and adopting a sedentary behavior, fewer fruits and vegetables consumption is expected,[22] it is therefore imperative that a methodological effort is made in order to quantify the extent of this change on the diet and make it a priority within public actions.

Including SQ and shorter versions of FFQ as part of the assessing consumption of foods and later monitoring and evaluation of nutrition programs would give advantages for the follow up, giving the perspective of where the interventions for health promotion should be.

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Mini Review

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The Bioactive Compounds in Medicinal Mushrooms have Potential Protective Effects against Neurodegenerative Diseases

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ABSTRACT

The Comprehensive and Alternative Medicine (CAM) to treat Neurodegenerative Diseases (NDs) has attracted attention from healthcare professionals and scientific researchers recently. Although in its early research stage, a good number of studies have been performed to investigate the potential preventive or even therapeutic effects of some medicinal mushrooms on NDs. We reviewed recent scientific publications reporting the extraction and identification of the bioactive compounds in medicinal mushrooms commonly used in Asian countries for their potential protective effects against NDs. Five medicinal mushrooms - *Hericium erinaceus, Termitomyces albuminosus, Ganoderma lucidum, Dictyophora indusiata, Mycoleptodonoides aitchisonii*- have been covered in this review. *In vitro*, *in vivo*, and clinical studies have been conducted to confirm the potential protective effects of these compounds against neurodegenerative diseases. Because of the limited research, no clear mechanisms of the preventive actions can be proposed. More animal and human studies are needed in the future to confirm the anti-neurodegenerative effects and understand the mechanism of the protective action of these bioactive compounds.

KEYWORDS: Neurodegenerative Diseases; Mushrooms; Neurite; Bioactive Compounds; Anti-oxidative effects.

ABBREVIATIONS: ND: Neurodegenerative Diseases; AD: Alzheimer's disease; PD: Parkinson's Disease; HD: Huntington's Disease; NGF: Nerve Growth Factor; BDNF: Brainderived neurotrophic factor; ER: Endoplasmic Reticulum.

INTRODUCTION

Neurodegenerative Diseases (NDs) are incurable and debilitating conditions that result in progressive degeneration and/or death of nerve cells. This causes problems with movement (called ataxias), or mental functioning (called dementias), most commonly seen diseases including Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD). Currently, there is no effective treatment that can cure NDs, the treatments can only delay the progression of the diseases for a short term. Therefore, the prevention of the NDs occurrence also attracts researchers' interests. One hypothesis of the pathogenesis of these diseases is proposed as increased free radical generation, and the consequent elevated oxidative stress in neural system.[1] For other types of chronic diseases such as cancer, epidemiological, animal, and *in vitro* studies show that the consumption of plant source food can potentially reduce the risk of neurodegenerative diseases attributing to the high anti-oxidative capacity of bioactive compounds in these foods. Mushrooms have been recognized as a healthy functional food because of the high protein and low fat content as well as their phytochemical components like vitamin D and polyphenols.[2-4] Mushroom-derived phytochemical components have anti-oxidative

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effects and have been confirmed to have therapeutic effects on some chronic diseases like cancer. Researchers deduce that the bioactive compounds in medicinal mushrooms can potentially reduce the risk of NDs *via* similar action principles.

The potential anti-neurodegenerative actions of medicinal mushrooms have been intensively investigated in numerous animal and cell line studies. In addition to the well-studied polysaccharides such as β-glucan, many small molecules are under investigation for the potential health beneficial effects. The mechanistic studies show that bioactive compounds in various medicinal mushrooms can inhibit activities of neurotransmitter enzyme, stimulate neurite growth, or play a role on anti-inflammatory and anti-oxidative activities.[5] In this review, we summarize the small bioactive molecules in various medicinal mushrooms that potentially carry the function of reducing oxidative stress in neural systems.

BIOACTIVE COMPOUNDS IN MEDICINAL MUSHROOMS POTENTIALLY AGAINST NEURODEGENERATIVE DISEASES

Hericium Eerinaceus

Hericium erinaceus has the common names as Lion's mane mushrooms or Pom Pom mushrooms, which is also a culinary mushroom in Asian countries. A clinical trial of daily consumption of 2.88 g *H. erinaceus* fruiting body dry powder for 16 wks has been performed in 30 Japanese men and women at age 50-80 years old who were diagnosed with mild cognitive impairment. The treatment can significantly (p<0.001) improve the cognitive function scale score (mean=27) of the mushroom-treated patients compared to the controls (mean=24) with no adverse effect detected.[6] Similar clinical trials have been performed in senior patients (average age is 75 for treatment group and 77.2 for controls) diagnosed with Parkinson's disease, degenerative orthopedic disease, cerebrovascular disease, etc. Oral administration of 5 g/day *H. erinaceus* dry powder for 6 months improved 6 out of 7 dementia patients' perceptual capacities.[7]

Hericenones (A-H) and Erinacines (A-K & P-Q), originating from fruiting bodies and mycelia respectively, are identified as the bioactive compounds that induce Nerve Growth Factor (NGF) synthesis both *in vitro* and *in vivo*.[5,7] Dilinoleoylphosphatidylethanolamine (DLPE) from fruiting bodies of *H. erinaceum* reduces oxidative stress in Endoplasmic Reticulum (ER) of Neuro-2a cells. 100 ng/ml DLPE significantly (p<0.005) reduced cell viability of Neuro-2a cells treated with tunicamycin, demonstrating the protective effects against oxidative stress.[8]

Termitomyces Albuminosus

Termitomyces albuminosus is consumed as edible mushrooms in many Asian countries such as China, Japan, Singapore as well as South American countries like Chile. This mushroom is also called Termite mushrooms or "Ji Zong" mushrooms in Chinese. Cerebrosides named termitomycesphins A, B, C, D, G, and H have been extracted and identified from dried fruiting bodies of *T.albuminosus*. The treatment of 10 μg/ml termitomycesphins A-D for 6 d and 1 μM G and H for 48 hrs increase rat pheochromocytoma PC12 cell neurite outgrowth by 20% and 20-50%, respectively.[9-10] Five fatty acid amides termitomycamide A, B, C, D, and E have been isolated from the same mushrooms. The treatment of 0.1 μg/ml termitomycamide B and E can significantly (p<0.01) reduced ER stress-induced Neuro-2a cell death by 20%.[11] The animal and human studies of this mushroom against neurodegenerative diseases are lacking.

Ganoderma Lucidum

Ganoderma lucidum is a widely used medicinal mushroom in Asian countries with the common name "Ling Zhi" in Chinese. It has been traditionally used to treat many chronic diseases such as cancer, diabetes, hypotension, insomnia, etc. There are numerous bioactive compounds that have been found in *G. lucidum*, including triterpinoids, nucleotides, sterols, steroids, fatty acids, etc. Many *in vitro* and *in vivo* studies demonstrate the neuroprotective effects of the bioactive compounds, however, the clinical trial to examine the neuroprotection of *G. lucidum* is lacking. The mechanistic studies show that the bioactive compounds can regulate aging-related gene to elongate yeast lifespan, and increase neurotrophin such as Nerve Growth Factor (NGF) and Brainderived neurotrophic factor (BDNF) to protect the neuronal cells death induced by serum deprivation.[12-14]

Dictyophora Indusiata

Dictyophora indusiata is an edible as well as medicinal mushroom in Asian countries. This mushroom has the common names as Veiled lady mushrooms or Bamboo mushrooms. Although it has a long history of being consumed in Asian countries, the investigation of the bioactive compounds associated with neurodegenerative diseases is very limited. Until now, dictyophorine A and B have been isolated from the mushroom and can significantly improve the amount of Nerve Growth Factor (NGF) in astroglial cells.[15] A more recent study identified dictyoquinazol A, B, and C in *D. indusiata*, and found that 5 μM dictyoquinazol A, B, and C treatment can reduce excitotoxin-induced cortical cell death. The protective effect is in a dose-dependent manner with ~20% for 0.5 μM and >60% for 5 μM.[16]

Mycoleptodonoides Aitchisonii

Mycoleptodonoides aitchisonii is an edible mushroom that is called "Bunaharitake" in Japanese. This mushroom is a rare type that has been consumed, which may be the reason that it has not been well investigated for the potential preventive effect against human diseases. Some bioactive compounds have been isolated and identified in this mushroom (Table 1). The treatment of 0.1 μg/ml 3-(hydroxymethyl)-4-methylfuran-2(5H)-one and (3R,4S,1'R)-3-(1'-hydroxy-ethyl)-4-methyldihydrofuran-2(3H)-one for 24 hrs significantly (p<0.01) reduced tunimycin-induced Neuro-2a cell death, indicating the protective

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effect against Endoplasmic Reticulum (ER) stress-induced cell death.[17] The treatment of 0.6 µM 5-hydroxy-4-(1-hydroxyethyl)-3-methylfuran-2(5H)-one and 5-phenylpentane-1,3,4-triol for 24 hrs has the same protective effect to the aforementioned bioactive compounds on ER stressed Neuro-2a cells.[18] The investigation on this mushroom is currently performed only *in vitro*.

The bioactive small molecules from the aforementioned medicinal mushrooms are summarized in Table 1.

FUTURE RESEARCH

Neurodegenerative disease is difficult to be cured by using the current available therapies. The prevention or delay this disease progress becomes an important therapy. The investigations of isolating and identifying the effective bioactive compounds in medicinal mushrooms that potentially prevent the neurodegenerative disease occurrence provide promising scientific data to demonstrate the potential of medicinal mushrooms as a prevention or treatment to the disease. The studies of the bioactive compounds in these mushrooms are still in early investigation stage. In addition to the aforementioned bioactive compounds in the medicinal mushrooms, various anti-oxidants have been reported in different mushrooms for their potential therapeutic effects on neurodegenerative diseases. For example, mushroom-derived ergothioneine has been confirmed to have anti-oxidative effects *in vitro* and *in vivo*.[19,20] One recent animal study showed oral administration of ergothioneine improved memory and learning abilities of Alzheimer's disease (AD) model mice.[21] Until now, most studies have been only performed in cell lines or animal models. Medicinal mushrooms are traditionally consumed in Asian countries. Very limited data come from human studies. Meanwhile, the investigations of certain bioactive compound are not well established. For many potential bioactive compounds, only one or two publications reported the data from very limited experiments.

Mushroom	Compound	Protection	References
Hericium erinaceum	Hericenones (A-H)	Induce NGF synthesis	5,7
	Erinacines (A-K & P-Q)		
	Dilinoleoyl-phosphatidylethanolamine (DLPE)	Reduce oxidative stress in ER	8
Termitomyces albuminosus	Termitomycesphins A, B, C, D,	Increase neuron cell growth	9
	Termitomycesphins G and H	Promote neurite growth	10
	Termitomycamide B and E	Reduce oxidative stress in ER	11
Ganoderma lucidum	Ganodermaside C and D	Regulate aging-related gene UTH1 in yeast and prolong the lifespan	12
	Ganodermaside A and B	Regulate aging-related gene UTH1 in yeast and prolong the lifespan	13
	Ganolucidic acid A	Have BDNF-like neurotrophic activities	14
	Ganoderic acid S1	Have BDNF-like neurotrophic activities	14
	Ganodermic acid TQ	Have BDNF-like neurotrophic activities	14
	Methyl ganoderic acid A and B	Have BDNF- and NGF-like neurotrophic activities	14
	Ganodermatriol	Have BDNF-like neurotrophic activities	14
	7-oxo-ganoderic acid Z	Have BDNF-like neurotrophic activities	14
	4,4,14-trimethyl-5-chol-7,9(11)-dien-3--oxo-24-oic aci	Have BDNF-like neurotrophic activities	14
Dictyophora indusiata	Dictyophorine A	Promote NGF synthesis	15
	Dictyophorine B	Increase NGF secretion level	15
	Dictyoquinazol A	Protect cortical neurons from excito-toxicity	16
	Dictyoquinazol B	Protect cortical neurons from excito-toxicity	16
	Dictyoquinazol C	Protect cortical neurons from excito-toxicity	16
Mycoleptodonoides aitchi-sonii	3-(hydroxymethyl)-4-methylfuran-2-(5H)-one	Protect Neuro-2a cells from ER stress	17
	(3R,4S,1'R)-3-(1'-hydroxy-ethyl)-4-methyldihydrofuran-2(3H)-one	Protect Neuro-2a cells from ER stress	17
	5-hydroxy-4-(1-hydroxyethyl)-3-meth-ylfuran-2(5H)-one	Protect Neuro-2a cells from ER stress	18
	5-phenylpentane-1,3,4-triol	Protect Neuro-2a cells from ER stress	18

Table 1: Bioactive compound in medicinal mushrooms that potentially have anti-neurogenerative effects.

It is worth to notice that mushrooms have been traditionally used as medicinal foods in some countries for the therapeutic effects. Meanwhile, the scientific research confirmed multiple potential therapeutic bioactive compounds in mushrooms, which indicates the whole food consumption is an effective approach for the health improvement purpose. However, more investigations on the bioavailability, efficacy, and interactions of bioactive compounds of the whole food are needed to confirm the concept.

Based on the current literature review, both *in vitro* and *in vivo* studies are needed for further investigation on the anti-neurodegenerative effects of the bioactive compounds; further mechanistic studies are needed to provide evidence for these compounds to be potential therapies against neurodegenerative diseases.

CONFLICTS OF INTEREST

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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