

Therapeutic role of L-DOPA produced as a secondary metabolite from different legumes and plant sources

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Abstract

L-DOPA (L-3,4-dihydroxyphenyl-L-alanine) is an important intermediate of secondary metabolism in higher plants and also a kind of important nerve transmitter which increases the dopamine content and obtains the therapy efficacy for the treatment of Parkinson's disease, a degenerative disorder. L-DOPA extract has been shown to significantly increase the body's natural production of human growth hormone and has various powerful health benefits for both men and women. L-DOPA can also act as a precursor for the synthesis of catecholamines. L-DOPA occurs naturally in seedlings, pods and beans of *Vicia faba* Linn. and in the seeds of *Mucuna pruriens* Baker, non DC. and is known as the major substance in the allelopathy of velvet bean plant, released from its roots. The presence of L-DOPA was previously thought in *Mucuna* and *Vicia* plants only. But now-a-days, it is also isolated from many other plants beyond these two genera.

Key words: L-DOPA (3, 4-dihydroxyphenyl-L-alanine), Parkinson's disease, Alkaloids, Velvet bean

Introduction

Most agronomic research was emphasized to increase the production of food and fiber in the last century (Abelson, 1994). However, during the last decade, more attention was focused on the production of new and alternative crops, which could be used in the development of products for pharmaceutical and other industries (Kumar, 2009). Legumes are playing an axial role in the conventional diets of human being throughout the world. Apart from common legume seeds, the nutritive potential of certain wild legume grains includes the pulses of tribal utility (Vadivel and Biesalski, 2012). L-DOPA (3, 4-dihydroxyphenyl-L-alanine) is an amino acid isolated from various legumes and plant sources in many forms, but not found in the animal body. Miller *et al.* (2009) reported that the L-DOPA (levodopa) is found in various kinds of food and herbs (*e.g.*, *Mucuna pruriens*, or velvet bean) as a naturally occurring dietary supplement and psychoactive drug form. It has been synthesized from the amino acid

L-tyrosine in the mammalian body and brain (Miller *et al.*, 2009 and Haq and Ali, 2006). According to the previous studies (Miller *et al.*, 2009; Peaston and Weinkove, 2004 and Nagatsu *et al.*, 1964), L-DOPA has been considered as the important precursor for the various neurotransmitters like dopamine, noradrenaline and adrenaline collectively known as catecholamines. L-DOPA has found wide spread application for symptomatic relief of Parkinson's disease (Ali *et al.*, 2005). Parkinson's disease is a degenerative disorder that causes rigidity, tremors, slowness of speech and eventually dementia. This also causes the changes in enzymes of energy metabolism of the myocardium, followed by the neurogenic injury (Lee *et al.*, 1996 and Lee *et al.*, 1999). Parkinson's disease has been associated with a diminished level of dopamine in the brain and is commonly treated by oral administration of L-DOPA, which is a precursor of dopamine, as the L-DOPA can transverse the blood brain barrier while the dopamine cannot. The success of L-DOPA application stimulated neurochemical research into all the neurodegenerative diseases (Lee *et al.*, 1996 and Lee *et al.*, 1999).

Synthesis of L-DOPA

L-DOPA has found to be produced by the amino acid, L-tyrosine and the reaction is mainly catalyzed by tyrosinase (EC 1.14.1.18.1). L-tyrosine is also the precursor for other

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catecholamines which are produced in the chromaffin cells of the adrenals, sympathetic nerve cells, and the neurons of various parts of the brain. Tyrosine uptake occurs *via* a transport carrier located in the blood brain barrier in the brain in competition with other neutral amino acids such as tryptophan, phenylalanine, leucine, isoleucine, and valine (Kumar *et al.*, 2006). L-tyrosine is a non-essential amino acid and synthesized in the body from phenylalanine. It acts as an intermediate in the synthesis of various biomolecules of the nervous system like L-DOPA, dopamine, epinephrine, norepinephrine, melanin, serotonin and also significant component of positive acute phase proteins synthesized by the liver. Another toxic compound, benzene can also be used as raw material for L-DOPA synthesis by using tyrosine phenol lyase enzyme. It can be a good economical alternative for the L-DOPA synthesis (Kumar and Azmi, 2007). The chemical synthesis of L-DOPA involves the use of several chemicals and catalysts under adverse production conditions. Alternate procedures for the L-DOPA production are: (i) its extraction from biological sources, (ii) its production by enzymes and intact microbes (Lee *et al.*, 1996 and Lee *et al.*, 1999). An enhanced product formation rate can be provided by these methods in most economic way under mild process conditions.

L-DOPA has been found to occur naturally in seedlings, pods and beans of *Vicia faba* Linn. (Broad bean) and in the seeds of *Mucuna pruriens* Baker, non DC. (Velvet bean). The first report on the production of L-DOPA from L-tyrosine by fungi was given by Sahi *et al.* (1969). Further Haneda *et al.* (1974) used another fungus *Aspergillus oryzae* for the conversion of L-tyrosine to L-DOPA, produced by the one-step oxidation reaction from L-tyrosine. The reaction was catalysed by tyrosinase, tyrosine hydroxylase or α -tyrosinase in living organisms (Rasazza *et al.*, 1974). Tyrosinases are widely distributed in nature and have been purified to homogeneity from both microbial and plant sources (Kim *et al.*, 1997). Tyrosinases are also known to exist in several fungi, such as *Neurospora crassa* (the red bread mould) and *Agaricus*

bispora (the cultivated button mushroom) and have been used for production of L-DOPA from L-tyrosine (Loganathan, 1998). However, in micro-organisms, tyrosinase activity has been generally found to be very weak as L-tyrosine and L-DOPA are rapidly decomposed to other metabolites. L-DOPA oxidized to form bonds with sulfur containing compound and polymerize with other amino acids, which is considered as the main reason of lower bioavailability of protein when L-DOPA is consumed *via* foods (Vadivel and Pugalenti, 2010). L-DOPA in legumes get destroyed by cooking and soaking with alkaline solutions (Echeverria and Bressani, 2006 and Vadivel and Pugalenti, 2010). However, the L-DOPA from *Mucuna pruriens* degraded by basic cooking but, roasting does not appear to destroy it (Dahouda *et al.*, 2009).

Sources of L-DOPA

Previously, the presence of L-DOPA was thought only from two plant genera; *Mucuna* and *Vicia*. Besides these two genera, potential of other plants like *Phanera*, *Pileostigma*, *Cassia*, *Canavalia*, *Dalbergia*, *etc.* can also be exploited for the production of L-DOPA. However, higher amount of L-DOPA has only been noticed in *Mucuna* species (%): *Mucuna andreana* (6.3-8.9), *Mucuna birdwoodiana* (9.1), *Mucuna holtonii* (6.13-7.5), *Mucuna mutisiana* (3.9-6.8), *Mucuna pruriens* (1.25-9.16), *Mucuna pruriens* var. *utilis* (8.05), *Mucuna sloanei* (3.34-9.0) and *Mucuna urens* (4.92-7.4). Wichers *et al.* (1984) reported that DOPA was also synthesized by the hydroxylation of tyrosine by phenol oxidase in cultured cells of *Mucuna pruriens*. High L-DOPA content in *Mucuna* seeds has been increasing their utilization as a food and feed.

L-DOPA from Velvet bean

Mucuna pruriens commonly known as ‘velvet’ bean (Figure 1), is an important tropical legume, found in bushes and damp places and scrap jungles throughout the plains of India. From the ancient time, the seeds of *M. pruriens* are used as a tonic and aphrodisiac for male virility (Anon, 1962).

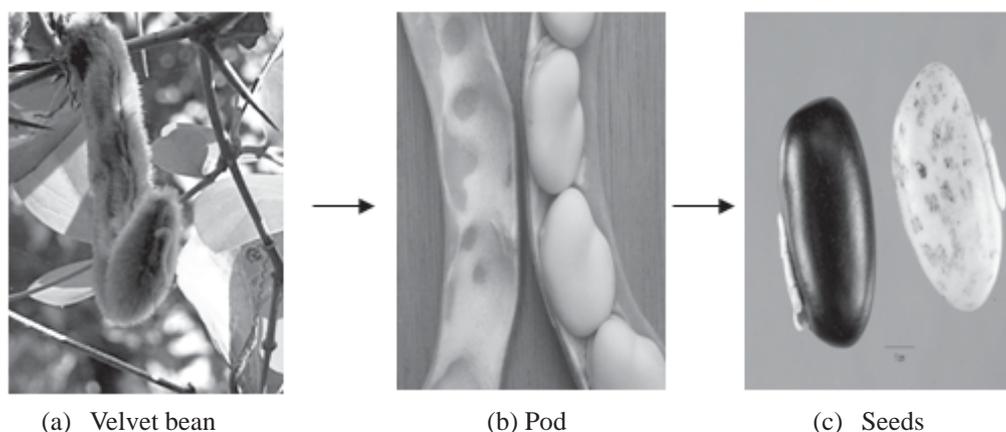


Figure 1: *Mucuna pruriens* (Velvet bean)

The occurrence of the catecholic amino acid 3-(3, 4-dihydroxyphenyl)-L-alanine (L-DOPA) attracted attention for the utilisation of the *M. pruriens* plant for L-DOPA production (Bell and Janzen, 1971 and Daxenbichler *et al.*, 1971). The presence of L-DOPA in several cell lines of suspension cells of *M. pruriens* has also been demonstrated (Wichers *et al.*, 1989 and Chattopadhyay *et al.*, 1994). However, the great demand for L-DOPA is largely met by the pharmaceutical industry through extraction of the compound from wild populations, but commercial exploitation of this compound is hampered because of its limited availability. All parts of *Mucuna* possess valuable medicinal properties (Caius, 1989), and there is a heavy demand of *Mucuna* in Indian markets. After the discovery L-DOPA in *Mucuna* seeds, its demand in international markets have increased by many fold (Farooqi *et al.*, 1999) and the demand has motivated Indian farmers to start commercial cultivation. A conventional method of propagation is limited to seeds, which causes several problems because of allergic properties that cause uncontrolled itching (Verma *et al.*, 1993 and Krishnamurthy *et al.*, 1996) and poor viability.

L-DOPA from Banana plant

Nagatsu *et al.* (1972) reported the formation of catecholamines in banana plants by phenol oxidase enzyme, which is different from animal tyrosine hydroxylase. It has been generally believed that either polyphenol oxidase or tyrosinase is involved in betacyanin biosynthesis in plants (Mueller *et al.*, 1996 and Steiner *et al.*, 1999). Some polyphenol oxidases as well as tyrosinase can convert tyrosine to DOPA and have the ability to oxidize DOPA to DOPA quinone. Tyrosinase was reported to be involved in betalain biosynthesis in higher plants by Steiner *et al.* (1999).

L-DOPA from purslane

Portulaca oleracea (Purslane) is an ornamental plant, widely growing in temperate climates which grows up to 30 cm tall, used generally as a medicinal plant in traditional medicine and food. *Portulaca oleracea* is a rich source of omega-3

fatty acids, galloannins, kaempferol, quercetin and apigenin and contains abundant catecholamines, noradrenalin (NA) and dopamine (DA) that were demonstrated to be the major bioactive constituents. Due to this plant being rich in protein, flavonoid, dopamine and noradrenaline has a great therapeutic use as antiseptic, diuretic, antipyretic, antioxidants. It also strengthen the immune system and acts as blood purifier (Simopoulos, 2004).

L-DOPA from *Acacia nilotica* and other sources

The seeds of *Acacia nilotica* (commonly known as black thorn tree), having admirable nutritional value received more attention (Vadivel and Biesalski, 2012). It is widely distributed throughout the tropical and subtropical regions of the world. In India, young pods and mature seeds of *A. nilotica* are known to be cooked and eaten by tribal people, living in Western Rajasthan (Janardhanan *et al.*, 2003). Polyphenol oxidase (PPO) is widely distributed in plants kingdom and considered as an important enzyme for the production of polymers and L-DOPA (Kazandjian and Klibanow, 1985). It has been suggested that enzyme might be associated with many other important function such as defence (Bouthyette *et al.*, 1987; Tremolieres and Bieth, 1984; Mayer and Harel, 1979 and Shaw *et al.*, 1991). Mushroom PPO was also used for the production L-DOPA and it can also inhibit selectively the growth of pigmented human melanoma (Wick, 1977). Banana is an important fruit crop in tropical countries. So far, there have been very few reports on PPO of Banana. Galeazzi *et al.*, (1981) has purified and characterized PPO from Banana fruit. However, There have been no reports on PPO in other tissues. The leaf and stem are agrowaste which might be a rich source of PPO. Seven different wild legume seeds (*Acacia leucophloea*, *Bauhinia variegata*, *Canavalia gladiata*, *Entada scandens*, *Mucuna pruriens*, *Sesbania bispinosa* and *Tamarindus indica*) from various parts of India (Table 1) were analyzed for total free phenolics, L-DOPA, phytic acid and their antioxidant capacity (ferric-reducing antioxidant power [FRAP] and 2,2-diphenyl-1-picrylhydrazyl [DPPH] assay) and type II diabetes-related enzyme inhibition activity (α -amylase).

Table 1: Some important plant sources for the production of L-DOPA

S.No.	Plants	Locations	Quantity of L-DOPA	References
1	<i>Mucuna Pruriens</i>	Young seeds Young leaves	0.53%- 1.19% 0.5%.	Vadivel and Pugalenth, 2010 and Tomita and Yokotan <i>et al.</i> , 2004
2	<i>Canavalia gladiata</i>	seeds	4.22%	Gautam <i>et al.</i> , 2012
3	<i>Bauhinia variegata</i>	seeds	2.91%	Gautam <i>et al.</i> , 2012
4	<i>Acacia leucophloea</i>	seeds	2.39%	Gautam <i>et al.</i> , 2012
5	<i>Entada scandens</i>	seeds	1.67%	Gautam <i>et al.</i> , 2012
6	<i>Sesbania bispinosa</i>	seeds	4.25% or 2.01%	Gautam <i>et al.</i> , 2012
7	<i>Tamarindus indica</i>	seeds	3.78%	Gautam <i>et al.</i> , 2012
8	<i>Prosopis Chilensis</i>	-	-	Ramya and Thaakur, 2007

S. bispinosa had the highest content in both total free phenolics and L-DOPA, and relatively low phytic acid when compared with other seeds. Phytic acid content, being highest in *E. scandens*, *M. pruriens* and *T. indica*, was highly predictive for FRAP assays. The phenolic extract from *T. indica* and L-DOPA extract from *E. scandens* showed significantly higher FRAP values among others (Gautam *et al.*, 2012).

Production of L-DOPA

L-DOPA extract of *Mucuna* plant (wild variety) has been used by the pharmaceutical industries to manage large market demand of L-DOPA. But at commercial level, its production has been found to be very low because of its limited availability. *Mucuna* plant is annual herbaceous plant which grows only from seeds and cannot be propagated by cuttings. But this problem can be solved by micropropagation technique which provides a rapid and large scale multiplication of the plant. The various attempts for the large scale production of L-DOPA have been made, using callus culture (Brain, 1979) and cell suspension (Huizing *et al.*, 1985; Wichers *et al.*, 1989 and Chattopadhyay *et al.*, 1994).

Production of L-DOPA was studied in cell suspension culture of *Mucuna pruriens* f. *pruriens*. Suspension culture was established in Murashige and Skoog's medium (Murashige and Skoog's, 1962) composed of half concentration of Murashige and Skoog's salts and 2% sucrose. A two-stage cell suspension culture was developed for enhanced accumulation of L-DOPA. In the first stage, the culture system was composed of MSI medium without CaCl_2 , which was suitable for cell growth and in the second stage MSI medium containing $42.5 \text{ mg.l}^{-1} \text{ KH}_2\text{PO}_4$ and 4% sucrose favoured L-DOPA production (Chattopadhyay *et al.*, 1994). Recently, Yamamoto *et al.* (2001) described the separation of tyrosine hydroxylase activity from polyphenol oxidase activity and the purification of tyrosine hydroxylase from betacyanin producing callus cultures of *Portulaca grandiflora* Hook (Portulacaceae). However, it remains a possibility that polyphenol oxidase in *P. grandiflora* may be able to hydroxylate L-tyrosine to L-DOPA, as well as to oxidize L-DOPA to DOPA quinone. Enantiomerically pure L-DOPA was produced from L-tyrosine in a single-step biotransformation process, using callus cultures of the plant, *P. grandiflora*. Callus cultures were induced in Murashige and Scoog's medium, provided with growth regulators such as benzylaminopurine and 2,4-dichlorophenoxyacetic acid and were found to be an excellent source of tyrosinase, which in turn was used for the biotransformation of L-tyrosine into L-DOPA (Rani *et al.*, 2007).

Extraction and estimation of L-DOPA

The extraction and estimation of L-DOPA can be done by a non-aqueous titration method described in British Pharmacopoeia (1980). The same method is recommended by

United State Pharmacopoeia with determination of L-DOPA by potentiometric end point and extractive procedure, followed by UV assay (Rockville, 1987). The estimation of L-DOPA in plants was done by using high performance liquid chromatography and reversed-phase high performance liquid chromatographic (Parikh *et al.*, 1990 and Siddhuraju *et al.*, 2001). Mennickent *et al.* (2007) has been reported a quantitative estimation of L-DOPA in tablets by high performance thin layer chromatography (HPTLC) and Modi *et al.* (2008) also described this technique for measurement of L-DOPA from *M. pruriens*. The HPTLC method requires long time for development of TLC plate, which is considered as the major disadvantage of this method. Kim *et al.* (2008) also reported simultaneous determination of levodopa and carbidopa by synchronous fluorescence spectrometry, using double scans. Another simple, accurate, reproducible and cost effective spectrofluorimetric method for the estimation of L-DOPA, from the seed of *M. pruriens* was also reported by Shah and Joshi (2010).

High performance thin-layer chromatographic (HPTLC) method for estimation of L-DOPA

L-DOPA, extracted from seeds of *Mucuna*, is a constituent of more than 200 indigenous drug formulations and is more effective as drug than the synthetic counterpart. A densitometric high performance thin-layer chromatographic (HPTLC) method was developed for quantification of L-DOPA content present in the seeds extract. The method involves separation of L-DOPA on precoated silica gel 60 GF₂₅₄ HPTLC plates, using a solvent system of n-butanol-acetic-acid-water (4:1:1, v/v) as the mobile phase. Quantification was done at 280nm, using absorbance reflectance mode. The method was validated for accuracy, precision and repeatability. The proposed HPTLC method was found to be precise, specific and accurate for quantitative determination of L-DOPA. It can be used for rapid screening of large germplasm collections of *Mucuna pruriens* for L-DOPA content. The method was used to study variation in fifteen geographical regions (Raina and Khatri, 2011).

Spectrophotometric method for estimation of L-DOPA

Estimation of L-DOPA was done spectrophotometrically according the procedure reported by Arnou (1937) and Jimenez-Hamman and Saville (1996), with the small modification. According to this method, the rate of conversion of L-tyrosine to L-DOPA was monitored spectrophotometrically after every 2 h of incubation. For estimation of L-DOPA, 1mL each of the reagents; 2M HCl, 15% (w/v) sodium molybdate, 15% (w/v) sodium nitrite, and 2M sodium hydroxide, was added to 1ml of culture supernatant. The acid is added to inactivate the residual free enzyme and stopping further biotransformation reaction (Pialis and Saville, 1998). Addition of sodium hydroxide turns

the yellow colour of the reaction mixture to an orange-red colour due to diazotization of the amino group of L-DOPA and the concentration of L-DOPA formed, was detected at 460nm in a spectrophotometer after 30 min from the standard curve of L-DOPA (Rani *et al.*, 2007).

Spectrofluorimetric method for the estimation of L-DOPA

According to this method of the extraction of L-DOPA from the seeds of *M. pruriens*, seeds of the plant were dried in shade and powdered in a mechanical grinder. The fats of *M. pruriens* seeds powder were removed with petroleum ether (60-80°C). Then aqueous extract was prepared by cold maceration method from the defatted powder. After seven days, the extract was filtered, using Whatman filter paper (No. 1) and then concentrated in vacuum and dried. L-DOPA content of concentrate was estimated using a spectrofluorometer (Shah and Joshi, 2010).

Role of L-DOPA in therapy

Most of the herbal materials used in the preparations of herbal medicines are derived from wild sources. The herbal extract of L-DOPA (an amino acid) has shown large number of health benefits. L-DOPA is primarily known for its conversion into dopamine. Dopamine plays important role in our body metabolism and required for the proper functioning of the brain. The numerous health benefits of L-DOPA extract have been investigated for over 50 years. Furthermore, if the L-DOPA is extracted from a natural plant sources, our body can easily absorbs and utilizes a higher percentage of it. The high absorption percentage of L-DOPA gives better results, because the natural of L-DOPA extracted from plants has no side effects (<http://www.organic-herb.com>).

Role of L-DOPA in the cure of Parkinson's diseases

James Parkinson wrote the first clinical description of the eponymous disease, now commonly referred as idiopathic Parkinson's disease in 1817. Parkinson's disease (PD) is a chronic neurological disorder, caused by a progressive degeneration of the nigrostriatal dopamenergic neurons of the basal ganglia. As the neurons in the ganglia degenerate, there is a loss of the neurotransmitter dopamine. When the individual initiates an action such as walking, the basal ganglia help smooth the movements and coordinate the posture by signaling the thalamus in the brain which then communicates with the cerebral cortex. All of these signals are coordinated by neurotransmitters and the neurotransmitter used by the basal ganglia is dopamine. As the neurons degenerate in PD, the level of dopamine is decreased and the number of nerve connections with other nerve and muscle cells also decreases. Levo-dopa (L-DOPA) is the precursor of dopamine and is widely used in the treatment of PD. However, it loses effectiveness as the disease progresses and has negative side effects. Parkinson's disease is characterized by the

presence of bradykinesia, muscular rigidity, rest tremor and postural instability (Hughes *et al.*, 1992). It is the second most common neurodegenerative disease, as Alzheimer's is the first (Kasture, 2009 and Abde-Salam, 2008). Apparently, the neurons in the ganglia degenerate due to oxidative stress which causes among other things an energy crisis in the mitochondria in the neurons. Parkinson's disease is a serious neurological disorder of the central nervous system that usually becomes apparent after the age of 55 (Murray, 1996). Dopamine itself cannot cross the blood brain barrier, if injected as such to the patients. So, instead of dopamine, biologically active molecules like L-DOPA are administered to the patients, suffering from neuropsychiatric disease. Levodopa (L-DOPA) is a commercially available precursor to dopamine and can replace the dopamine lost due to nigrostriatal cell degeneration (Kumar, 2009).

Role of L-DOPA on hormones regulation

Although L-DOPA is well known for its role in the treatment of Parkinsons, it has many other beneficial effects on human health. L-DOPA extract has been significantly increasing the production of human growth hormone naturally. This is very important property of L-DOPA because increasing in the level of human growth hormone has powerful health benefits for both men and women. It is the most potent hormone in the human body and it controls the ageing process. When L-DOPA has been administered orally, it found to increase levels of growth hormone in humans significantly (Hanew *et al.*, 1998; Schonberger *et al.*, 1977; Schonberger *et al.*, 1976 and Tharakan *et al.*, 2007). L-DOPA and dopamine have also been shown to inhibit prolactin, a hormone that suppresses male testosterone production. Prolactin has a positive correlation with a second hormone called somatostatin, which decreases the both amount and effectiveness of circulating growth hormone. Therefore, by lowering prolactin (and consequently somatostatin) levels, human growth hormone increases both testosterone and GH production; leading to greater recovery (Vaidya *et al.*, 1978). Dopamine crosses the blood/brain barrier poorly, and cannot exert optimal effects on target receptors unless enough of the compound reaches the brain. L-DOPA is freely absorbed across this barrier, and when L-DOPA crosses the barrier readily, growth hormone levels increase (Hanew *et al.*, 1998; Schonberger *et al.*, 1977; Schonberger *et al.*, 1976; Fevang *et al.*, 1977; Philippi *et al.*, 2000 and Tharakan *et al.*, 2007). L-DOPAA is most effective when conversion of L-DOPA to dopamine is mediated by a decarboxylase inhibitor. A decarboxylase inhibitor is a substrate that inhibits the metabolism of one biological entity into another biological entity (Hanew *et al.*, 1998; Schonberger *et al.*, 1977; Schonberger *et al.*, 1976; Fevang *et al.*, 1977; Philippi *et al.*, 2000; Xiao *et al.*, 2008 and Bertoldi *et al.*, 2001). The administration of L-DOPA in rats (human dose equivalent 160mg/kg) is associated with the increased circulating

testosterone level in them (Yamada *et al.*, 1995). The other study investigating testosterone levels is done in Japanese Quails, which shows increased testosterone possibly secondary to dopaminergic influence of the testes (Prasad *et al.*, 2009). 0.5g L-DOPA has been associated with increasing levels of circulating growth hormone in persons without hypopituitarism, after ingestion (Root and Russ, 1972). This increase in growth hormone has been replicated elsewhere (Boden *et al.*, 1972). In rats, an oral dose of 1000mg/kg bodyweight (human dose equivalent 160mg/kg) increases Luteinizing hormone after 4 hours, yet it returns to baseline after 8 hours (Yamada *et al.*, 1995). This effect was neither seen at 200mg/kg (32mg/kg humans) nor any dose below (Yamada *et al.*, 1995). Ingestion of 500mg L-DOPA in human actually causes a slight but significant decrease in circulating Luteinizing Hormone levels over the 2 hours, following treatment (Boden *et al.*, 1972). A recent study in persons with Parkinson's disease suggests that after ingestion of 200mg L-DOPA (paired with 50mg benserazide), there will be reduction in cortisol levels (Mullar *et al.*, 2007). L-DOPA administration at 800mg daily for 7 days in healthy men (no complaints of penile problems) is associated increased penis tumescence; however, its effects were most significant when serum testosterone was greater than 17.5pg/mL suggesting the effect is androgen-dependent (Horita *et al.*, 1998).

Adverse effect of L-DOPA on health

L-DOPA has been found to cause abnormal motor control (Drug-Induced Dyskinesia), which is seen as a common side effect when L-DOPA is used chronically for treating Parkinson's disease. A loss of dopamine in the Basal Ganglia is associated with a process called dyskinogenesis. Dyskinogenesis involves the involuntary movement of skeletal muscles (Nadjar *et al.*, 2009). On the neuronal side of things, it is hypothesized that drug-induced dyskinesia is due to sensitization of the D1 (dopamine-1) receptors on the messenger neurons in the striatum (Feyder *et al.*, 2011). High sensitization leads to intermittent and excessive cAMP signalling cascades, and involuntary movement. Interestingly, tolerance to caffeine is associated with desensitized D1 receptors on this neuronal cluster and may be used to manage symptoms of involuntary motor control associated with L-DOPA supplementation (Prediger, 2010). However, for healthy persons, the importance of being concerned with levodopa induced dyskinesia is unknown.

Conclusion

L-DOPA has been considered as the most powerful drug available in the market for the treatment of Parkinson's disease and hormonal imbalance. Though the DOPA can be prepared by chemical synthesis rapidly, but the reaction results in the racemic mixture (DL) of the product which was found to be inactive. Further separation of pure L-DOPA from this racemic

mixture was found to be very difficult. D-DOPA interferes with the activity of DOPA decarboxylase, the enzyme involved in the production of dopamine in the brain. Hence, it is important to find out a one-step bioconversion process for transformation L-tyrosine into L-DOPA in very economical way. As the market demand for L-DOPA is very high due its therapeutic potential, its production by micropropagations is highly relevant. However, the plants can also be explored as alternative source for the extraction of L-DOPA with desired level of purity.

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