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Biological sources of L-DOPA: An alternative approach

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ABSTRACT

Parkinson's disease was first formally identified by British physician James Parkinson in 1817 as "The Shaking Palsy". L-DOPA (3,4-dihydroxyphenyl-L-alanine) has been considered as a gold-standard treatment for Parkinson's disease. The world market for L-DOPA is about 250 t/year and the total market volume is about $101 billion per year. The present review summarizes the different biological sources for the production of L-DOPA. The process for L-DOPA production from different biological sources has advantages over the chemical methods such as, enantiometrically pure L-DOPA, less incubation time and cost effective method. L-DOPA is found naturally in certain plant foods, particularly broad beans which found to replenish brain levels of L-DOPA even more quickly, and for longer periods, than conventional medication.

Keywords: Parkinson's Disease; L-DOPA; Biological Sources

1. INTRODUCTION

Parkinson's disease (PD) has been a constant challenge to public health around the world [1]. 3,4-dihydroxy phenyl-L-alanine (L-DOPA) is an amino acid analogue and drug of choice in the PD-a degenerative neurological disorder [2]. In the United States alone, about 1 million people are affected by PD and worldwide about 5 million. PD occurs among 1% of individuals aged 60 years while 4% of those 80 years old. The disease (PD) is characterized by progressive death of dopamine producing neurons in the basal ganglia of the brain [3-5]. Loss of the neurotransmitter dopamine can cause a number of effects, including rigidity (muscles resistant to movement), akinesia (inability to initiate movement), bradykinesia (slowness of movement), and rest tremor [4]. Many brain cells of PD patients contain Lewy bodies which are unusual deposits or clumps of the protein alpha-synuclein, along with other proteins. Researchers are unable to find out formation of Lewy bodies or their role in development of the disease. For many decades, there were no effective treatments for PD, and it was thought to be a terminal illness. But in the 1940s and 1950s, neurosurgeons began to perform surgery on the basal ganglia of brain which gave little cure in PD symptoms. Though surgery was effective, it was risky, with about 12 percent of patients dying as a result of operation. The biggest advancement in Parkinson's treatment came in the 1960s, when researchers identified low levels of dopamine in brain among diseased persons. This research revolutionized the treatment of PD, led to the development of levodopa, also called L-DOPA (Larodopa, Dopar), which is been used as medication [6]. L-DOPA can easily cross the blood–brain barrier and gets converted into dopamine, it can be administered orally to relieve the symptoms of PD [7]. Levodopa is still the cornerstone of Parkinson's treatment today.

Within the past three years, L-DOPA therapy has been considered as the subject of several extensive reviews by investigators in various parts of the world. The preliminary studies in both animals and humans date back to 1957 while first clinical trials to 1960 and 1961 [2]. This review summarizes the biological sources for L-DOPA production which can be used as an alternative for chemically synthesized drugs, surgery and multidisciplinary management against the disease.

2. BIOCHEMISTRY OF DOPAMINE

Interest in L-DOPA therapy for Parkinson's disease has been considerably enhanced since the recent release of this drug to all medical practitioners. Both experimental and clinical studies have suggested that the depletion of dopamine can be corrected by the administration

of L-DOPA either orally or intravenously. A level of homovanillic acid (the main breakdown product of dopamine) in the cerebrospinal fluid of patients before and after the administration of oral L-DOPA proves its applicability [2].

Parkinson's disease affects a part of brain called the "basal ganglia", which controls movement. Cells in the basal ganglia begin to degenerate as a result of the condition, and lose of their ability to produce a neurotransmitter (a chemical that carries messages between brain and nerve cells) called dopamine. As dopamine levels drop, the production of another neurotransmitter, called acetylcholine, increases. The balance between these two is critical, because they have opposite effects; acetylcholine stimulating muscle contraction, and dopamine damping it down. When the balance shifts in favour of acetylcholine, muscles become rigid with increasing jerky movements which are difficult to control this is often accompanied by tremors in hands. Whilst conventional drugs can be administered to control symptoms, they have a range of unpleasant side effects and cannot limit its progression. During the early stages of the disease, conventional drugs, called anticholinergics, can reduce symptoms of muscle rigidity and excess salivation by blocking the action of acetylcholine. However, they can cause dry mouth, constipation, anxiety, drowsiness and blurred vision. Whereas, direct administration of L-DOPA also has dangerous side-effects, including nausea, internal bleeding, palpitations, dizziness and depression because of it is being converted to dopamine before it reaches to brain.

3. L-DOPA TOXICITY

A number of PD patients treated with L-DOPA. Patients have to suffer a variety of side effects; most commonly are nausea, vomiting, low blood pressure and restlessness. The drug can also cause drowsiness or sudden sleep onset, which can make driving and other activities dangerous. The repeated pulsatile stimulation of striatal dopamine receptors with chronic oral L-DOPA treatment induces plastic changes in basal ganglia circuits that can lead to the development of motor response complications (MRC). A more pressing concern regarding L-DOPA is it causes hallucinations and psychosis after long-term use. Some patients exhibit severe dyskinesias soon after starting low doses of L-DOPA. There are controversies in the treatment, whether it causes the motor complications or it is toxic to dopaminergic neurons, but it has not yet been proven and clinical trials have not clarified this situation.

There were number of therapies have been developed to improve PD management, such as dopaminergic agonists, inhibitors of catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO-B). In combination therapy usually, patients are given levodopa combined with another substance called carbidopa (decarboxylase inhibitor). Addition of carbidopa lowers the amount of levodopa that is required and may reduce some of its side effects such as nausea and vomiting by reducing the supply of "free" dopamine outside the brain. Carbidopa delays the conversion of levodopa into dopamine until it reaches the brain, preventing or diminishing some of the side effects that often accompany levodopa therapy. It also reduces the amount of needed levodopa.

L-DOPA is very useful drug for reducing the tremors and other symptoms of PD during the early stages of the disease. It allows the majority of PD patients to extend their period of time of normal and productive lives. The dramatic improvement can be seen in PD patients after starting levodopa therapy. However, in order to get maximum benefit there is need to increase the dose gradually. A high-protein diet can interfere with the absorption of levodopa, so physicians recommend that patients shouldn't take protein-rich meals during their early stages of the treatment. L-DOPA therapy is necessary for PD patients as there is no other therapy provides more powerful antiparkinsonian effect.

4. SYNTHESIS OF L-DOPA

4.1. Chemical Synthesis

Chemical synthesis of L-DOPA involves use of extensive chemicals, catalyst under harsh production conditions [8-10]. Resultant L-DOPA by the process is racemic DL mixture, which is inactive and to separate enantiometrically pure L-DOPA is very difficult. The recemic mixture was easy to obtain but difficult to separate by the time it has been resolved, the projected costs doubled. Monsanto's position in vanillin, which provided the L-DOPA moiety, found that they were custom manufacturing a recemic intermediate, which was done by deblocking to L-DOPA according to Hoffman-LoRche. The synthesis, which followed closely the Erlenmeyer azlactone procedure described in organic synthesis, went by way of a pyrochiral enamide, which was hydrogenated to block DL-DOPA [11,12]. Currently in the market the available tablets for L-DOPA are under various brand names Sinemet®, Atamet®, Parcopa® and Stalevo®. More over L-DOPA obtained from mentioned chemical methods was found to be with 90% recovery.

4.2. Biological Sources

Until the middle of the 20th century, the amino acid 3,4-dihydroxyphenylalanine (L-DOPA) was just seen as an intermediate in the biological synthesis of melanin and epinephrine. In the earliest 1960s, it was proved that, L-DOPA is a neurotransmitter precursor has wide therapeutic applications [9]. There were many biological sources reported for enantiometrically pure L-DOPA (**Table 1**).

Table 1. Different Biological sources for L-DOPA production.

Biological sources	Yield of L-DOPA	References
Enzymatic synthesis		
E. intermedia cells (polyacrylamide gels)	5.4 $g \cdot l^{-1}$	[16]
E. intermedia cells (carrageenan gel)	7.8 $g \cdot l^{-1}$	[17]
Mushroom tyrosinase (Nylon 66)	0.143 g	[18]
Chitosan flakes Non optimized batch reaction optimized batch reaction	 44.86 $mg \cdot l^{-1} \cdot h^{-1}$ 54 $mg \cdot l^{-1} \cdot h^{-1}$	[19]
Mushroom tyrosinase (zeolite)	36 $mg \cdot l^{-1} \cdot h^{-1}$	[20]
Modify *poystryene* PSNH PSCL	 1.39 mg 1.99 mg	[21]
Cu-alginate	4.5 $mg \cdot l^{-1} \cdot h^{-1}$	[22]
Mushroom tyrosinase On PEI On activated on agar blocks On activated agar particles	 25 mg 42 mg 73 mg	[23]
Fungi		
Aspergillus oryzae IAM2625	0.88 g	[24]
Stemonitis herbicola	50 mg	[25]
Aspergillus oryzae (mutant)	1.28 mg/ml	[26]
Aspergillus oryzae	1.28 mg/ml	[27]
Aspergillus oryzae UV7(double mutant)	1.28 mg ml	[28]
Aspergillus oryzae	1.86 mg/ml	[29]
Aspergillus oryzae UV-7	444 g cells	[30]
Aspergillus oryzae ME2 (Illite)	1.686 mg/ml	[31]
Aspergillus oryzae ME2 (Celite)	0.428 mg/ml	[32]
Aspergillus oryzae (Double mutant)	300 mg	[33]
Aspergillus oryzae IIB-6	1.34 mg/ml	[34]
Acremonium retilum	0.89 mg/ml	[35]
Aspergillus niger	0.365 mg/ml	[36]
Actinomycetes	28.6%	[37]
Yeast		
Yarrowia lipolytica NRRL-143	2.96 mg/ml	[38]
Egyptian *halophilic* black yeast	66 ug/ml	[39]
Bacteria		
Vibrio tyrosinaticus	4 mg/ml	[40]
Pseudomonas melanogenum	8 mg/ml	[41]
E. coli W(ATCC 11105) (p-hydroxyphenyl acetate 3-hydroxylase)	48 mM in reaction mixture	[42]
Bacillus sp. JPJ	0.497 mg/ml	[7]
Recombinant *Erwinia herbicola* cells strain AJ2985	15 g/l/h	[45]

Continued

Brevundimonas sp. SGJ	3.81 mg/ml	[43]
Brevundimonas sp. SGJ	3.361 mg/ml	[44]
Plants		
Mucuna atterrima	4.5%	[46]
Mucuna pruriens	-	[47]
Tissue cultures of Banana	-	[53]
Vicia faba (Fava bean)	3.4 mg/g DW	[52]
Stizolobium hassjoo	2 g/l	[54]
Mucuna pruriens	3.54% DW	[48]
Mucuna pruriens var utilis (velvet bean)	6.36% W/W	[49]
Stizolobium hassjoo	495 mg/ml	[55]
Portulaca grandiflora	48.8 mg/l/h	[56]
Mucuna pruriens	24 g/DW	[50]
Mucuna monosperma	5.48% DW	[51]

The production of L-DOPA from biological sources involves the oxidation of L-tyrosine by enzyme tyrosinase (E.C.1.14.18.1), which is copper containing enzyme widely distributed in plants, animals and microorganisms [13]. Oxidation product of tyrosinase subsequently converted in to melanin; as it functions like alternative substrate for tyrosinase ultimately stimulate catalytic efficiency. This cresolase and catecholase mechanisms occurs in melanin synthesis pathway in microorganisms, while in brain naturally the L-tyrosine is converted in the epinephrine finally by the series of enzymatic reactions initiated with tyrosine hydroxylase [14]. The process for the synthesis of L-DOPA form different species is carried out using various methods.

4.2.1. Enzymatic Synthesis

Mushroom tyrosinase has been commercially used in the enzymatic synthesis of L-DOPA by enzyme immobilization [15]. It lowers the production cost due to the reusability of the enzymes. The various techniques used for enzyme immobilization include entrapment in polymeric gels, adsorption onto insoluble materials, encapsulation in membranes, cross-linking with bifunctional or multifunctional reagents and linking to an insoluble carrier [16-23]. The substrate used for the synthesis of L-DOPA were catechol, sodium pyruvate and ammonium acetate.

4.2.2. Fungal Sources

Mostly, L-DOPA from fungal species was obtained in the reaction mixture containing substrate L-tyrosine and mycelia in the buffer. Briefly, the mycelia were suspended in reaction mixture containing L-tyrosine, L-ascorbic acid and intact mycelia under optimized condition. In addition, specific additives were used as elicitors for enhanced yield of L-DOPA. L-DOPA produced by the method was enantiometrically pure as well as it is cost effective. Similarly, biotransformation of L-DOPA from L-tyrosine was carried out using *Acremonium reticulum* by submerged fermentation process yields more amount of L-DOPA in the broth [24-37]. Production of L-DOPA also reported from yeast species [38,39].

4.2.3. Bacterial Sources

L-DOPA produced from different bacterial species includes both in broth as well as in buffer with substrate and acclimatized cells. Initially, the medium optimization was performed in order to maximum production of L-DOPA. To overcome the tedious downstream processing after production of L-DOPA by this process, use of acclimatized cells with buffer gave the best results within less time and experimentation [7,40-44]. In case of L-DOPA production using enzymatic process of recombinant *E. herbicola* cells carrying a mutant transcriptional regulator TyrR yield obtained was near about 15 $g \cdot l^{-1} \cdot h^{-1}$ [45]. This mechanism of synthesis is now accepted commercially by the industry named as Aginomoto CO.LTD.

4.2.4. Plants

Plants were exploited as an alternate source for the isolation of L-DOPA and in a screening survey; more than 1000 species in 135 plant families have been screened. Genus *Mucuna* (Leguminosae) was found to contain the maximum level of L-DOPA which has been successfully exploited commercially [46-51]. Among the various species of *Mucuna*, *M. holtonii*, *M. pruriens* and *M. monosperma* were having promising L-DOPA content

in their seeds. Fava bean (*Vicia faba*), seed sprouts, pods, and broad beans are one of nature's best plant sources of L-DOPA widely cultivated legume, commonly consumed and have anti-Parkinson's effect [52]. Shoot and callus cultures of banana showed accumulation of L-DOPA when the culture supplemented with tyrosine and phenylalanine. Bananas are grown in many developing countries all over the world and the fruit is known to have soothing effect in the nervous system [53]. There are many plant sources reported for L-DOPA production [54-56].

5. CONCLUSION

Most of the L-DOPA isolated is either from natural sources or synthesized chemically, but biological sources could be used as an alternative source for L-DOPA production. The alternative sources of L-DOPA and a further clinical trial will open the subject of extensive research. Chemical synthesis methods were time consuming, required costly and toxic chemicals like catechol, pyrocatechol and also resulted in recemic mixture of L-DOPA. Biological synthesis of L-DOPA will be the most promising approach to overcome ill-effects of chemical drugs. Different sources like enzymatic, fungal, bacterial and plant, yield maximum amount of enantiometrically pure L-DOPA under optimized cultural conditions. Most of the plant sources belong to legumes which can be used for the consumption, along with their L-DOPA content; role of plant phenolics (antioxidants, antimutagens and scavengers of free radicals) becomes vital as far as total health is concerned. L-DOPA from natural sources reduces the secondary complications also helps to delay the progression of the disease. Taken together, most of the research on synthesis of L-DOPA has been done using biological sources but now it is necessary to find exact mechanism of action and chances to cure the Parkinson's disease in future.

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