Obacunone: An Essential Limonoid in Disease Prevention

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ABSTRACT
Obacunone is a highly oxygenated triterpenoid, which exists in citrus species of Rutaceae family. Effects on the pharmacology of the compound has gained much attention in the recent years. Though, there is no such thorough understanding based on the chemistry, sources, pharmacological and distribution, absorption and excretion studies of the compound. Therefore, the current review focusses on the up-to-date study and the necessary information on the therapeutic effectiveness of the compound and finding various ways out in order to expand the digestibility and solubility. Obacunone has shown a wide range of pharmacological effects in the anticancer and anti-inflammatory activity. Moreover, obacunone has some complex effects on the hepatotoxicity. Pharmacokinetic studies suggest the lower solubility, poor oral absorption and less bioavailability of this compound. We found out that the substitution in the position of obacunone is one of the key factors that are known to affect the pharmacokinetic behavior of the compound. Therefore, much more research and information are being required to understand how the concentration of obacunone affects the pharmacological behavior-one of the key factors that needs to be assessed properly.

Keywords: Obacunone, Bioavailability, Pharmacokinetics, Pharmacological

INTRODUCTION
Parkinson’s disease is the most widespread neurodegenerative disorder which is signalized by the accelerating deprivation in the dopamine-producing neurons in the particular portion of the brain called as substantia nigra. The exact cause of this disease is still unknown. The most prevailing mechanism is the oxidative stress, but the rising facts depicts that apoptosis and oxidative stress induced activation of mitochondrion-dependent cell loss appears to be accountable for the disease [1], [2], [3]. The signs for PD generate after a 60-65% neuronal loss has found to occur at substantia nigra and the 80-85% decrement of dopamine occurs at striatum [4]. The succession of the disease may differ from patient to patient. Studies have revealed that the mid time till the end rate of the disease from the commencement of the symptoms is 9-14 years. 50% decline in the disease progression will have a 35% drop off in the economic implications [5]. Till now no such treatment for Parkinson’s disease has gained an in sight. Medicaments are more often based on the reduction in the symptoms of neuro-degenerated dopaminergic neurons [6] and, therefore, existing strategies of research and medical treatment advancements have made their way towards the anticipation in the loss of dopaminergic neurons [7].
Obacunone, a natural compound which is basically derived from citrus fruits. It is found to exhibit various anticancer, anti-proliferative, cytotoxic activities and anti-aromatase activity. Obacunone and their glycosides are found to inhibit carcinogenesis through chemically induced methods and cancer cell lines of humans with its cytotoxic action against the skin, oral, lung and colon cancer [8]. Hamster cheek pouch model has been used for the testing of three components mainly (obacunone, deoxylimonin and ichangensin) for the chemo-preventive activity of cancer [9]. In-vivo studies have shown that limonoids like (obacunone, nomilin and limonin) helps in the inhibition of aberrant crypt foci in colon cancer [10], [11]. In addition, few studies have shown that obacunone treatment has found to accelerate the mechanism of apoptosis by the upregulation in the expression of Bax which is pre-apoptotic protein and down-regulating the Bcl2 anti-apoptotic protein also in the induction of the G1 phase of the cell cycle. Obacunone has shown to exert an anti-inflammatory response by targeting the inhibition of (MIF) for the regulation of (MKP-1) pathway mitogen activated protein kinase phosphatase 1 [12]. Obacunone exhibited the protective mechanism against the ulcerative colitis in mice by the modulation of gut microbiota [13]. In-vivo studies have depicted that on administration of obacunone, there has been a strong inhibition for the bleomycin instigated lung fibrosis in mice [14].

At present, the effects of obacunone on its pharmacology are attracting lot of attention for the researchers. In the coming years most of the investigations have been carried out depicting the pharmacological effects of obacunone, and plentiful of the advancements are still needed. These antiviral and antioxidant effects. Modern pharmacological effects reveal the value of obacunone in the treatment of diseases like; hepatitis, cancer brain aging, obesity, enteritis [15],[16].

However, in the upcoming years, some studies have depicted that obacunone exhibits genotoxicity. Meanwhile, in terms of pharmacokinetics, low bioavailability, poor oral absorption and complex effects on liver enzyme metabolism of obacunone have engrossed its importance. The purpose of this review is to make the people aware about the chemistry, sources with the latest advances in the pharmacokinetics and the pharmacological effects of obacunone, as it will help in discovering the remedial importance of this compound and to discover novel ways out for enhancing the its pharmacological activity.

**Chemistry & Sources**

The citrus-derived obacunone, a natural occurring triterpinoid and limonoid is found in the barks of *Phellodendron chinense* [17] and is being isolated from the plants of *Citrus aurantium* L. and *Dictamnus angustifolius* [18], [19] which belongs to the family of *Rutaceae Juss* shown in Table 1. Some simple chemical modifications have been carried out on their functional groups which are considered for their biological activity. These groups include the C-7 carbonyl, which underwent reduction to the corresponding alcohol, and from which the oximes, acetates were prepared and the hydrogenation occurred in the furan ring with respect to the obacunone compound. This compound has found to inhibit the aromatase activity in an in-vitro enzymatic assay. The reference compound consists of four rings which is condensed in a steroid like fashion [20].

The compound exhibits reduction of 1 with sodium borohydride in the presence of diverse solvents such as CH3- CN, THF, CH2Cl2, and CH3OH. The ratio of C7a-hydroxyobacunone (2) and C7b-hydroxyobacunone isomers (3) was associated with the reaction mixture of the solvents [21].
This compound is highly oxygenated and modified terpenoids with an archetypal structure either containing a precursor with a 4,4,8-trimethyl-17-furanylsteroid skeleton belonging to the casimirolide class of organic compounds with the key substituents like Limonoid skeleton, Naphthopyran, Naphthalene, 1,4-dioxepane, Delta valerolactone, Dioxepane, Dicarboxylic acid or derivatives, Pyran, Oxane, Heteroaromatic compound, Furan, Alpha,beta-unsaturated carboxylic ester, Enoate ester, Lactone, Ketone and Carboxylic acid ester having chemical formula C26H30O7 [22] shown in Fig.1.

Fig.1 Chemical Structure of Obacunone

Table 1. Limonoids Containing Plants

<table>
<thead>
<tr>
<th>Family</th>
<th>Plant Material</th>
<th>Plant Species</th>
<th>Plant Part</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutaceae</td>
<td><strong>Auranti fructus</strong> Immitarus</td>
<td><em>Citrus aurantium</em> L. <em>Citrus sinensis osbeck</em></td>
<td>Fruits</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td><em>Citri reticulatae</em> Pericarpium</td>
<td><em>Citri reticulatae</em> Blanco.</td>
<td>Fruits</td>
<td>Peels [33]</td>
</tr>
<tr>
<td></td>
<td>Pummelo</td>
<td><em>Citrus maxima</em> (Burm) Merr.</td>
<td>Peels</td>
<td>[34]</td>
</tr>
<tr>
<td>Meliaceae</td>
<td><strong>Toosenden fructus</strong></td>
<td><em>Melia toosenden</em> Sieb. Et Zucc.</td>
<td>Fruits</td>
<td>[35]</td>
</tr>
</tbody>
</table>
Pharmacological Properties
Species rich in obacunone, limonoids, nomilin has found to reduce the formation of tumors by inhibiting the development of 7,12-dimethylbenz[a]anthracene. The group of workers used Hamster Cheek Pouch Model and after undergoing treatment with obacunone there was a significant reduction observed in the number of tumors by 25-40% respectively [23]. In one of the study 50kg of obacunone was administered orally and the anti-proliferative ability of the compound was analyzed by flow cytometry which resulted in the shortening of colon and arrested the G1 and G2 phase and suppressed the mode of action for the cell cycle genes in mice [24]. Limonin and obacunone are the limonoids found in the citrus species. Their altered effects were investigated on the development of aberrant crypt foci where the activity of detoxification enzymes such as quinone reductase, Glutathione S-transferase activity in male F344 rats were observed when treated with azoxymethane. Administration of obacunone and limonin resulted in 28-42% reduction in the yield of aberrant crypt foci. Thus, the study demonstrates the chemopreventive effects of the citrus limonoids on the chemically induced rat colon carcinogenesis [25].

Obacunone, a triterpenoid exhibits anti-inflammatory activities and has shown mechanisms in LPS-activated macrophages. The experiment showed the reduction in the number of pro-inflammatory mediators (e.g., IL-1β, IL-6, MCP-1 and NO) at the transcriptional and the translational level without exhibiting cytotoxicity. Detailed study of the mechanism demonstrated that there was the suppression observed in the p38 mediated AP-1 signaling as it was found to stabilize the messenger RNA of MKP-1 which is a mitogen-activated protein kinase phosphatase 1, thus increasing the expression time of the MKP-1 protein. After that on applying computational target-fishing technology, the possible targets of obacunone were predicted. The best interaction was confirmed between OBA and MIF which is a macrophage migration inhibitory factor. Therefore, the study concludes that obacunone plays a role as an anti-inflammatory agent by targeting intracellular macrophage inhibitory factor for the regulation of MKP-1/p38/AP-1 pathway [26].

Studies have shown the role of obacunone in amelioration of the inflammation in the intestine for the mouse model with ulcerative colitis. The said compound attenuated the excessive activation of TLR4 which is a toll like receptor and mediates nuclear factor kappa-B signalling. Obacunone indorsed the expression of occludin and TJP-1 and helped in repressing the activation of signalling cascades playing their role in the inflammation. Hence, owing to its abundance in the citrus fruits the biological importance of this compound has been taken into consideration due to which the anti-inflammatory effects of it are successfully proven [27].

Pharmacokinetics Study
Studies have shown that the limonoids have been distributed in the small intestine, duodenum and the rectal tissues of the rats, and amongst which the drug distribution kinetics have been much higher in

<table>
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<tr>
<th>Ranunculaceae</th>
<th>Coptis rhizoma</th>
<th>Coptis Franch</th>
<th>chinensis</th>
<th>Roots and Rhizomes</th>
<th>[36]</th>
</tr>
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</table>

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case of small intestine, and it has reached the maximum concentration peak within the duration of 3-4 hours after its administration. Researchers still believe that the citrus obacunone, a natural limonoid has been successful in exerting its therapeutic effect in the rat’s intestinal tissue through the intestinal absorption locally [28]. Further, the research has confirmed the absorption of the limonoids via the mechanism of diffusion, but uncertainly the absorption was saturated and poor. This poor oral absorption may be due to the participation of cytochrome CYP3A4 and P-glycoprotein [29].

Owing to its low solubility, the bioavailability of the limonoids is very less [30]. The distribution profile of the limonoids in dogs and rat have given an indication about the poor absorption of the compound. It takes a much longer time to reach the blood concentration at its peak value but as soon as it enters the blood, the metabolism of the limonoid is gradually achieved and the half-life is shortened. The bioavailability of the limonoid could be enhanced as per the study demonstrated when absorption enhancer like sodium dodecyl sulfate and borneol were ingested orally with the citrus limonoid as they can meaningfully impact the pharmacokinetic behavior of the limonoid compound, amongst which the rate of absorption of the limonoid was increased in the intestine of the rats, for which the area under maximum plasma concentration (C_{max}) and concentration–time curve (AUC) of limonoid showed an increased peak. Therefore, it was believed that the P-glycoprotein might be an important cause for absorption enhancing agents, promoting the distribution and absorption of the limonoids [31].

**Conclusion & Future Prospectives**

Obacunone is abundant in plant resources and exists widely in most of the traditional medicines that are known to possess high medicinal importance, in the anti-inflammatory, anticancer, anti-bacterial and anti-viral treatment, having immense clinical application. *In-vitro* and *In-vivo* studies have revealed that obacunone helps in regulating the expression of related proteins, including p53, p21, MCP-1. The compound also affects TLR4/NF-κB, Wnt5/beta-catenin, and TLR signaling pathways. This review discusses about the mechanism of obacunone in the treatment of Parkinson’s disease. Therefore, there is an urgent need to have a detailed study on the current issues based on the aforementioned research findings.

Studies based on the drug absorption, distribution and excretion have revealed the lower solubility, poor absorption and low bioavailability owing to its, ability to activate the mechanism of action of p-glycoprotein. The replacement of C-7 position of obacunone has some important characteristics and novel structure derivatives can effectively improve the anti-inflammatory, anti-viral and anti-microbial properties, thereby it could show the higher solubility in water for the enhanced bioavailability. Hence, it is a matter of concern and a belief that the structural alteration of obacunone will be the cyanosure of futuristic research.


