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RESEARCH ARTICLE

Substantiating the mechanism of Boswellic acids through molecular docking study

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ABSTRACT

Inflammation is the first response shown by the immune system in defense to any attack by bacteria or viruses. Inflammation is responsible for contributing to half of the world's global burden of disease. It is mainly characterized by pain (dolor), heat (calor), swelling (tumor), and redness (rubor). The inflammatory cascades are the sole reasons for many musculoskeletal disorders. These musculoskeletal disorders are prevalent throughout the world, with a ubiquitous impact leading to long-term pain and disability. They significantly affect the psychosocial status of people who have them. Boswellic acids (BA), a natural mixture isolated from oleo gum resin of *Boswellia serrata* comprised of four major pentacyclic triterpene acids: Beta-BA, 3-acteyl beta BA, 11-keto-beta-BA, and 3-acetyl-11-keto-beta-BA, isolated from the oleo gum resin of *B. serrata* is reported to be effective as anti-inflammatory, immunomodulatory, anti-tumor, anti-asthmatic and in chronic colitis. Its anti-inflammatory activity has been attributed to the inhibition of 5-lipoxygenase in a selective, enzyme-linked non-redox, and non-competitive manner. The anti-asthmatic reports on BA revealed that leukotriene and elastase enzyme inhibition might be responsible for this effect. Although BA acts through several mechanisms for its biological activities, the inhibition of leukotrienes is the primary and the most scientifically proved mechanism. This work substantiates the effect of *B. serrata* BAs through molecular docking study into the cavity of 5-LOX enzyme.

KEY WORDS: Boswellic acid, *Boswellia serrata*, anti-inflammatory , molecular docking, 5-LOX

INTRODUCTION

B. serrata (Family: *Burseraceae*), also called Salai guggal or Indian olibaum, is a branching tree found in dry mountainous regions of India, the Middle East, and Northern Africa.[1] It has an important place in the ancient Indian literature for the treatment of various inflammatory diseases such as osteoarthritis, rheumatoid arthritis, inflammatory bowel disease, and Crohn disease.[2] The plant exudate, which is obtained by making an incision in the trunk of the tree known as Salai, is an oleo gum resin known to have anti-inflammatory, antiarthritic, and analgesic properties.[3]

B. serrata extract (BSE) also has a pivotal role in preventing the degradation of articular cartilage by reducing the degradation of glycosaminoglycans. BSE thus shows superiority over currently used NSAIDs, which are well-known to accelerate articular damage in conditions of arthritis.[4] Besides, it also assists 3-acetyl-11-keto-β-boswellic acid (AKBA) in inhibiting the products of inflammatory process such as oxygen radicals and enzymes such as human leukocyte elastase, thereby minimizing the destruction of tissues.[5]

B. serrata is available in the market in the form of ointments, creams, and capsules. The first marketed preparation of *B. serrata* came in India under the trade name of Sallaki; it

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was later imported to Switzerland under the trade names of H15 Gufic, Sallaki, and H15 Gufic.[6]

This oleo gum resin is composed of 30–60% resin, 5–10% essential oils, and 12–23% mucus. The resinous part contains monoterpenes, diterpenes, triterpenes, pentacyclic triterpenic acids, and tetracyclic triterpenic acids. Main active constituents present in the oleo gum resin are basically pentacyclic triterpene acids (Boswellic acids [BAs] 30%): β-BA, 3-acteyl-β-BA, 11-keto-β-BA, and AKBA, as depicted in Figure 1.[7] BAs are mixture comprised of pentacyclic triterpene acids isolated from the oleo gum resin of *Boswellia serrata* that is reported to be effective as anti-inflammatory agent.[8]

In view of above reports, exhaustive work has been done on BA for its biological activity and mechanism of action. Hence, it was thought desirable to substantiate the anti-inflammatory activity of BA, we docked it against 5-LOX.

MATERIALS AND METHODS

A series of three BAs (3-acetyl-beta-boswellicacid, 11-keto-beta-BA, and AKBA)[9] and standard 5-LOX inhibitor zileuton,[10] namely, were sketched in ChemDraw Ultra 16.0. All designed compounds were further processed and investigated by Autodock Vina.[11]

Protein and ligand preparation

The 3D structure of 5-LOX protein (PDB ID: 6NCF) embedded with AKBA as cocrystallized ligand was downloaded from the rcsb database as shown in Figure 2.[12] The selected protein was subjected to protein preparation in Autodock 4.2 software. The protein preparation includes deleting ligand (AKBA); addition of hydrogen atoms. In addition, water molecules were deleted and polar hydrogen was added. After that, add Kollman charge and save the file in.pdbqt format.

The structures of synthesized compounds were imported into the Chem3D software and converted in.sdf format and then.sdf format were imported in pymol to convert it in.pdb

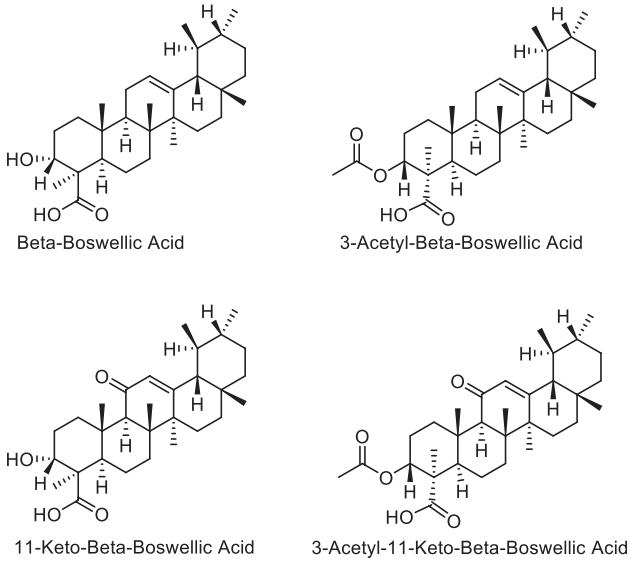

Figure 1: Structures of Boswellic acids.

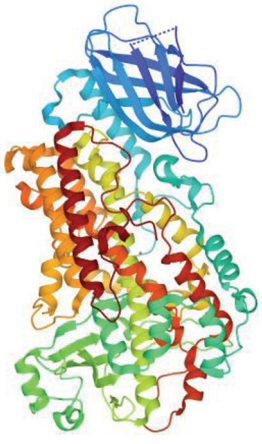

Figure 2: 3D structure of 5-LOX protein (PDB ID: 6NCF).

Table 1: Docking scores and interactions of compounds

Compound Code	Docking score (Kcal/mol)	Types of interactions
3-acetyl-beta-boswellicacid	2.036	Alkyl interactions with Pro621, Tyr100, Lys83, Tyr81, Phe402; Pi-Alkyl interactions with Pro621, Phe402; Hydrogen bond interactions with Gln611, Asp170, Ser171
11-keto-beta-boswellic acid	−3.192	Alkyl interactions with Pro621, Leu615, Tyr615, Tyr81, Lys83, Tyr100; Pi-Alkyl interactions with Leu615, Phe402; Hydrogen bond interactions with Gln611, Ser171
3-acetyl-11-keto-beta-boswellic acid	2.193	Alkyl interactions with Pro621, Tyr100, Lys83, Tyr81, Phe402; Pi-Alkyl interactions with Pro621, Phe402; Hydrogen bond interactions with Gln611, Asp170, Ser171
Zileuton	−6.194	Alkyl interactions with Arg401, Val367, Arg101, Ala388; Pi-Alkyl interactions with Val367, Arg101, Ala388; Hydrogen bond interactions with Tyr100, Gln168, Asp166, Trp102; Pi-Donor Hydrogen bond interactions with Tyr383; Pi-Sulfur interactions with Hie624 and Phe393

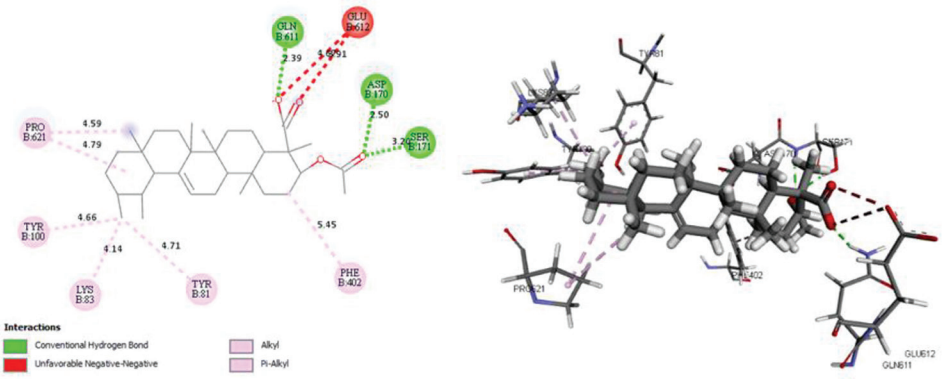

Figure 3: Interaction diagram of 3-acetyl-beta-boswellicacid inside cavity of 5-LOX protein (PDB ID: 6NCF).

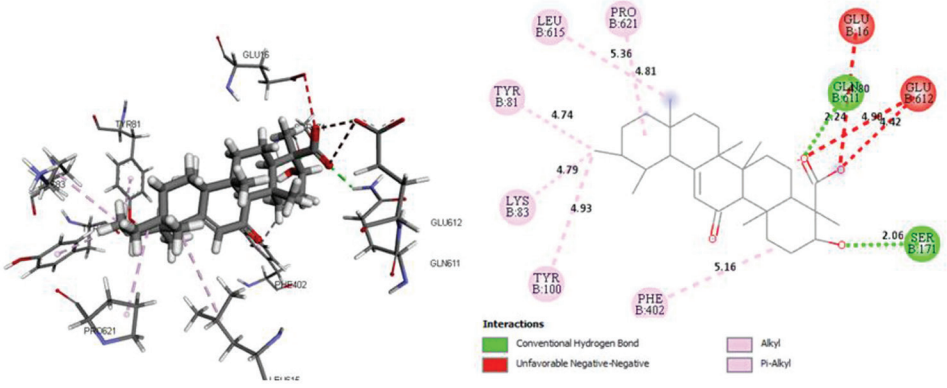

Figure 4: Interaction diagram of 11-keto-beta-boswellic acid inside cavity of 5-LOX protein (PDB ID: 6NCF).

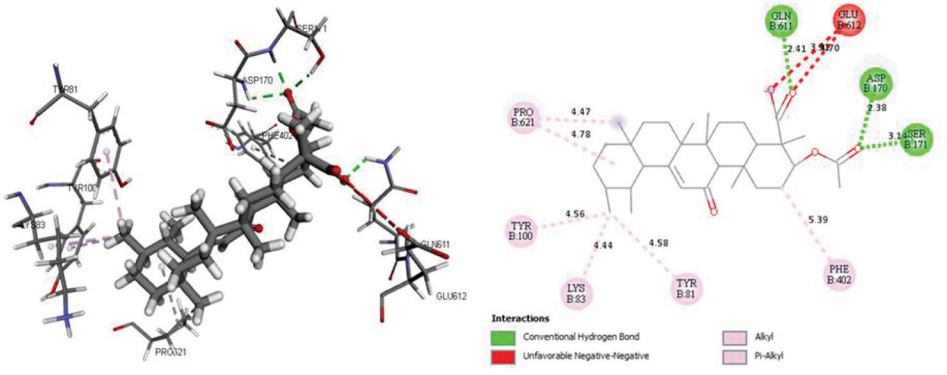

Figure 5: Interaction diagram of 3-Acetyl-11-Keto-Beta-Boswellic Acid inside cavity of 5-LOX protein (PDB ID: 6NCF).

format. Finally.,pdb format were imported in Autodock 4.2 for converting.pdbqt format.[13]

Docking protocol

Autodock 4.2 program has been used for docking. First, convert the ligand.pdb and protein.pdb file into ligand. pdbqt and protein.pdbqt format. After that dock in command prompt using commands. Log file and output.pdbqt file were generated. These two files have been open in Pymol and save the file. Then, open the saved file in Discovery studio 2021 software to see the 2D and 3D-Interaction. The Dock score values were calculated and interaction pose was saved for the study.[13,14]

RESULTS

From the docking studies, it was found that 11-keto-beta-BA possesses highest affinity toward 5-LOX with docking score of –3.192, whereas 3-acetyl-beta-boswellicacid and AKBA presented with docking scores of 2.036 and 2.193, respectively, compared to the standard 5-LOX inhibitor zileuton with docking score of -6.194

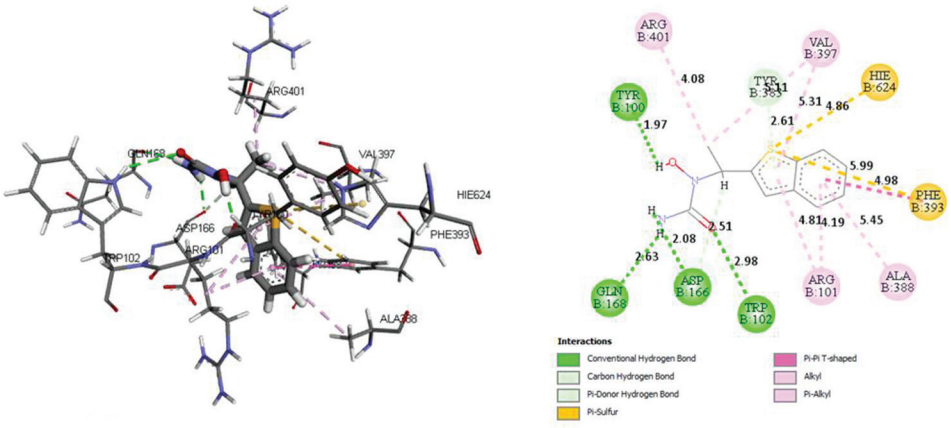

Figure 6: Interaction diagram of Zileuton inside cavity of 5-LOX protein (PDB ID: 6NCF).

(Table 1). Also, the 2D and 3D interaction diagram are shown in Figures 3-6.

CONCLUSION

As Indian herbal medicines are increasingly becoming popular worldwide, pharmacological evidences to understand the action of these medicines and the underlying mechanisms to support the proper and safe use of these medicines in clinic are indispensable.[15] They are commonly prescribed alone or in combination to achieve sufficient effect in complex conditions such as rheumatoid arthritis.[16,17] The results of this *in silico* molecular docking study revealed that the BAs (3-acetyl-beta-boswellicacid, 11-keto-beta-BA and AKBA) binded at the same cavity as that of standard 5-LOX inhibitor zileuton. The binding of BAs at the same cavity as that of zileuton is substantiated by their interaction with amino acid Tyrosine100. Although the docking scores were not as good as the zileuton, binding at same cavity as that of zileuton substantiates their mechanism of action by as 5-LOX inhibitors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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