International Journal of Pharmaceutical research and Applications
Volume 11, Issue 3, May-June2026, pp:1897-1902 www.ijprajournal.com ISSN:2456-4494

Comparative Molecular Docking Analysis of Beta vulgaris Phytocompounds and Aspirin Against Fc Gamma Receptors and Pro-inflammatory Cytokines

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Date of Submission: 10-06-2026 Date of Acceptance: 20-06-2026

Abstract

The current study investigates the immunomodulatory potential of phytocompounds identified in the hydromethanolic extract of Beta vulgaris (HMEBV) by comparing their molecular interactions with key immune receptors and cytokines against those of aspirin, a known anti-inflammatory agent. Using molecular docking, the binding affinities of six GC-MS-identified HMEBV compounds were evaluated against Fc gamma receptors I (FcγRI) and II (FcγRII), as well as the pro-inflammatory cytokines interleukin-1 (IL-1) and interleukin-6 (IL-6).Aspirin exhibited binding affinities of –60.93 kcal/mol and –52.60 kcal/mol for FcγRI and FcγRII, respectively. In contrast, HMEBV phytocompounds demonstrated stronger interactions, with 6-Octadecenoic acid, methyl ester showing –76.09 and –65.99 kcal/mol, and 9,12-Octadecadienoic acid (Z,Z), methyl ester showing –75.90 and –67.98 kcal/mol for the same receptors. Other constituents, including Methyl stearate (–70.31 and –68.08 kcal/mol) and Pentadecanoic acid, 14-methyl (–71.63 and –59.70 kcal/mol), also showed superior binding compared to aspirin.Similarly, aspirin bound to IL-1 and IL-6 with affinities of –61.64 and –55.66 kcal/mol, respectively. HMEBV compounds surpassed these values, with Methyl stearate (–75.30 and –68.47 kcal/mol), 6-Octadecenoic acid, methyl ester (–75.29 and –69.04 kcal/mol), and others exhibiting stronger interactions.These findings suggest that the HMEBV extract contains bioactive phytochemicals with a higher binding potential to key immune targets than aspirin. These results suggest that HMEBV contains compounds with potentially superior anti-inflammatory and immunomodulatory activities compared to aspirin, warranting further pharmacological evaluation.

Keywords: Molecular docking, Gas chromatography – mass spectrometry, inflammation, immune system

I. Introduction

Inflammation is a multifaceted and tightly regulated physiological process initiated by the immune system in response to harmful stimuli such as pathogens, damaged cells, or irritants. It involves the coordinated activation of immune cells and the release of various pro-inflammatory mediators, including cytokines, chemokines, and lipid-derived molecules (Medzhitov, 2008). Among these mediators, interleukins such as IL-1 and IL-6 play pivotal roles in orchestrating the inflammatory cascade by promoting leukocyte recruitment, fever, and acute-phase protein synthesis (Tanaka et al., 2014). In addition, cell surface receptors such as Fc gamma receptors (FcγRs), particularly FcγRI (CD64) and FcγRII (CD32), are integral in mediating antibody-dependent cellular responses, including phagocytosis, cytokine production, and antigen presentation (Nimmerjahn&Ravetch, 2008). Dysregulation of these pathways can contribute to chronic inflammatory diseases and autoimmune conditions.

Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, are widely used to manage inflammation and pain. Their primary mechanism of action involves the irreversible inhibition of cyclooxygenase (COX) enzymes, thereby reducing the biosynthesis of prostaglandins, which are key mediators of inflammation, fever, and pain (Vane & Botting, 2003). However, despite their

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Volume 11, Issue 3, May-June2026, pp:1897-1902 www.ijprajournal.com ISSN:2456-4494

efficacy, long-term or high-dose use of aspirin is frequently associated with gastrointestinal toxicity, renal dysfunction, and increased risk of cardiovascular events, which limit its use in chronic inflammatory conditions (Rothwell et al., 2012; Patrono et al., 2005).

In light of these limitations, attention has increasingly turned to natural products as alternative or complementary anti-inflammatory agents. Phytochemicals derived from medicinal plants are of particular interest due to their structural diversity, multi-target potential, and generally favorable safety profiles (Newman & Cragg, 2020). Beta vulgaris Linn. (beetroot), a plant rich in bioactive compounds such as betalains, flavonoids, phenolic acids, and nitrates, has been traditionally used for its antioxidant, hepatoprotective, cardiovascular, and anti-inflammatory properties (Georgiev et al., 2010; Clifford et al., 2015). Recent pharmacological studies have shown that beetroot extracts can attenuate inflammation through the modulation of NF-κB signaling, inhibition of pro-inflammatory cytokines, and suppression of oxidative stress markers (Kujawska et al., 2009; Domínguez et al., 2017).

This study investigated the molecular docking interactions between selected phytochemicals identified in the hydromethanolic extract of Beta vulgaris Linn (HMEBV), as characterized by gas chromatography–mass spectrometry (GC-MS), and key immune effectors involved in inflammatory signaling, specifically FcγRI, FcγRII, interleukin-1 (IL-1), and interleukin-6 (IL-6). Comparative docking analyses were also performed using aspirin as a reference compound. The aim is to assess the potential of HMEBV phytoconstituents to modulate immune and inflammatory pathways via high-affinity binding to these molecular targets, thereby providing mechanistic insight into the anti-inflammatory action of Beta vulgaris and supporting its development as a phytotherapeutic agent.

II. Materials and Methods

2.1 Phytochemical Profiling of HMEBV

GC-MS analysis was carried out using a gas chromatograph interfaced with a mass spectrometer, equipped with a capillary column (e.g., HP-5MS, 30 m × 0.25 mm, 0.25 µm film thickness). Helium was used as the carrier gas at a constant flow rate of 1.0 mL/min. A 1.0 µL aliquot of the extract, diluted in GC-grade methanol, was injected into the system using a split mode (10:1 split ratio). The injector temperature was set at 250°C. The oven temperature program was initiated at 60°C, held for 2 minutes, and then ramped at 10°C per minute to a final temperature of 280°C, which was maintained for 10 minutes. The mass spectrometer was operated in electron ionization (EI) mode at 70 eV, with a scan range of 50–650 m/z. The ion source and interface temperatures were set at 230°C and 280°C, respectively. The resulting chromatograms were interpreted using spectral libraries such as the National Institute of Standards and Technology (NIST) and Wiley libraries. Identification of compounds was based on a comparison of their mass spectral fragmentation patterns and retention times with those available in the databases. Each compound's molecular formula, molecular weight, and characteristic fragments were used to verify its identity.

2.2 Molecular Docking

Molecular docking was carried out using iGEMDOCK to evaluate ligand-receptor interactions. The target proteins—FcγRI (PDB ID: 1T83), FcγRII (PDB ID: 1FCG), IL-1 (PDB ID: 4DEP), and IL-6 (PDB ID: 1ALU)—were retrieved from the RCSB Protein Data Bank. Aspirin served as the reference ligand.After each compound was docked into the binding site, iGEMDOCK generated protein–compound interaction profiles of electrostatic (E), hydrogen-bonding (H), and van der Waals (V) interactions. Finally, the docked compounds were ranked by total energy of a predicted pose in the binding site that is defined as: (E/kcal mol−1) is: E = vdW + Hbond + Elec, where the vdW is van der Waal energy, Hbond is the hydrogen bonding energy, and Elect terms are electro statistic energy (Hsu et al., 2011). Thereafter, the molecular interactions between the proteins and the first two compounds with a lowest binding energy compared to the reference compound (aspirin) was viewed with Discovery Studio Visualizer, BIOVIA, 2024.

III. Results

Table 1 showed the identified Compounds in Hydromethanolic extract of Beta vulgaris L (Beetroot) and their properties through gas chromatography and mass spectrometry. The identified compounds include Pentadecanoic acid 14-methyl-, methyl ester ($C_{15}H_{30}O_2$) 9,12-Octadecadienoic acid (Z,Z)-, methyl ester ($C_{18}H_{32}O_2$), 9-Octadecenoic acid (Z)-, methyl ester ($C_{19}H_{36}O_2$), 6-Octadecenoic acid, methyl ester ($C_{18}H_{34}O_2$), Methyl stearate ($C_{19}H_{38}O_2$) and Heptasiloxane,1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethyl ($C_{14}H_{44}O_6$)

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Table 2 described the binding energy of ligands to FC gamma receptors, revealing aspirin to FcγRI (-60.93 Kcal/mol) and FcγRII (-52.60 Kcal/mol). Binding energy of phytocompounds identified in HMEBV through GC-MS to FcγRI and FcγRII respectively was revealed to be as follows: 6-Octadecenoic acid, methyl ester (-76.09 and -65.99), 9,12-Octadecadienoic acid (Z,Z) methyl ester (-75.90 and -67.98), 9-Octadecenoic acid (Z)-, methyl ester (-72.31 and -68.64), Heptasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethyl- (-58.76 and -61.54), Methyl stearate (-70.31 and -68.08), Pentadecanoic acid, 14-methyl (-71.63 and -59.70).

Table 3 described the binding energy of ligands to IL-1 and IL-6, revealing the binding energy of aspirin to IL-1 (-61.64 Kcal/mol) and IL-6 (-55.66Kcal/mol). Binding energy of phytocompounds identified in HMEBV through GC-MS to IL-1 and IL-6 respectively was revealed to be as follows: 6-Octadecenoic acid, methyl ester (-75.29 and -69.04), 9,12-Octadecadienoic acid (Z,Z) methyl ester (-74.65 and -67.97), 9-Octadecenoic acid (Z)-, methyl ester (-66.38 and -72.47), Heptasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethyl- (-58.13 and -60.58), Methyl stearate (-75.30 and -68.47), Pentadecanoic acid, 14-methyl (-66.96 and -68.86).

Table 1: Identified Compounds in Hydromethanolic Fruit extract of *Beta vulgaris L* (Beetroot) and their properties

S/N	Compound name	Chemical formula	Molecular weight (g/mol)	Retention Time (min)	% content
1	Pentadecanoic acid 14-methyl-, methyl ester	$C_{15}H_{30}O_2$	242.39	14.635	**31.526**
2	9,12-Octadecadienoic acid (Z,Z)-, methyl ester	$C_{18}H_{32}O_2$	280.45	16.253	4.620
3	9-Octadecenoic acid(Z)-, methyl ester	$C_{19}H_{36}O_2$	296.49	16.316	26.754
4	6-Octadecenoic acid, methyl ester	$C_{18}H_{34}O_2$	282.46	16.373	12.551
5	Methyl stearate	$C_{19}H_{38}O_2$	298.50	16.544	16.240
6	Heptasiloxane,1,1,3,3,5,5,7,7,9,9,11,11,13,13 -tetradecamethyl	$C_{14}H_{44}O_6$	505.09	17.837	8.309

Abundance

1.9e+07
1.8e+07
1.7e+07
1.6e+07
1.5e+07
1.4e+07
1.3e+07
1.2e+07
1.1e+07

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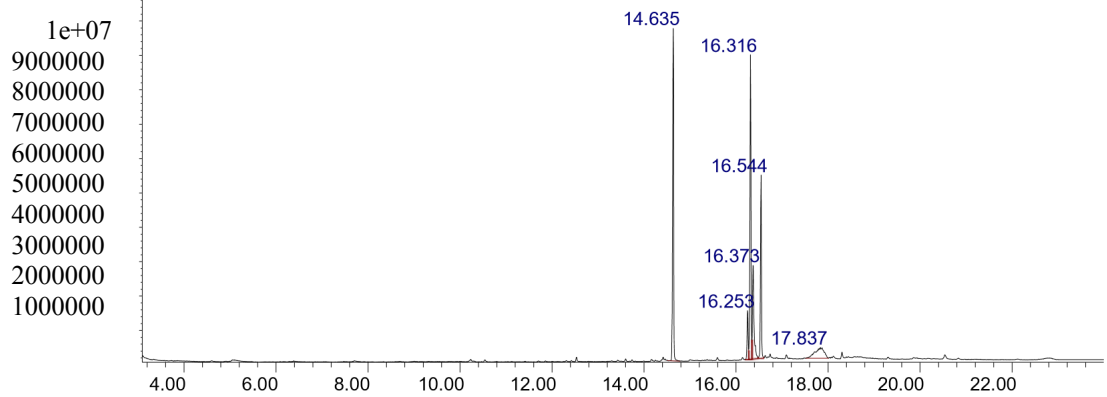

Figure 1: Total Ion Chromatogram (TIC) showing multiple peaks

Table 2: Binding Energy of ligands to FcγRI and FcγRII

S/N	Compounds	Binding energy (Kcal/mol)	
		FcγRI	FcγRII
R	**Aspirin**	**-60.93**	**-52.60**
1	6-Octadecenoic acid, methyl ester (Methyl oleate)	-76.09	-65.99
2	9,12-Octadecadienoic acid (Z,Z) methyl ester (Linoleic acid)	-75.90	-67.98
3	9-Octadecenoic acid (Z)-, methyl ester (methyl linoleate)	-72.31	-68.64
4	Heptasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethyl-	-58.76	-61.54
5	Methyl stearate	-70.31	-68.08
6	Pentadecanoic acid, 14-methyl	-71.63	-59.70

Table 3: Binding Energy of ligands to IL-1 and IL-6

S/N	Compounds	Binding energy (Kcal/mol)	
		IL-1	IL-6
R	**Aspirin**	**-61.64**	**-55.66**
1	6-Octadecenoic acid, methyl ester (Methyl oleate)	-75.29	-69.04
2	9,12-Octadecadienoic acid (Z,Z) methyl ester (Linoleic acid)	-74.65	-67.97
3	9-Octadecenoic acid (Z)-, methyl ester (methyl linoleate)	-66.38	-72.47
4	Heptasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethyl-	-58.13	-60.58
5	Methyl stearate	-75.30	-68.47
6	Pentadecanoic acid, 14-methyl	-66.96	-68.86

IV. V. Discussion

The molecular docking results presented in this study provide compelling evidence for the potential of phytocompounds derived from the hydromethanolic extract of Beta vulgaris (HMEBV) to modulate immune responses by targeting critical inflammatory mediators and immune receptors. Specifically, these phytoconstituents demonstrated notable binding affinities to Fc gamma receptors I and II (FcγRI and FcγRII), as well as to the pro-inflammatory cytokines interleukin-1 (IL-1) and interleukin-6 (IL-6), surpassing or closely

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approximating the binding energies exhibited by aspirin, a conventional non-steroidal anti-inflammatory drug (NSAID).

Aspirin, widely recognized for its anti-inflammatory and immunomodulatory properties, displayed binding affinities of -60.93 kcal/mol and -52.60 kcal/mol for FcγRI and FcγRII, respectively. These results align with its known capacity to modulate immune responses indirectly through inhibition of cyclooxygenase (COX) enzymes and prostaglandin synthesis (Vane & Botting, 2003). However, several phytochemicals identified via gas chromatography–mass spectrometry (GC-MS) in HMEBV, such as 6-Octadecenoic acid, methyl ester and 9,12-Octadecadienoic acid (Z,Z) methyl ester, showed stronger binding affinities to both FcγRI (-76.09 and -75.90 kcal/mol, respectively) and FcγRII (-65.99 and -67.98 kcal/mol, respectively), indicating a potentially more effective interaction with these receptors compared to aspirin.

Similarly, 9-Octadecenoic acid (Z)-, methyl ester and methyl stearate exhibited robust binding energies against FcγRI (-72.31 and -70.31 kcal/mol, respectively) and FcγRII (-68.64 and -68.08 kcal/mol, respectively), suggesting that these compounds may influence Fc receptor-mediated immune signaling pathways. Fcγ receptors are essential in antibody-dependent immune functions, including phagocytosis and cytokine release, and are critically involved in the pathogenesis of autoimmune and inflammatory disorders when dysregulated (Nimmerjahn&Ravetch, 2008). The ability of HMEBV phytoconstituents to bind these receptors with high affinity may therefore contribute to immunomodulatory and anti-inflammatory activities observed in traditional and experimental use of Beta vulgaris (Georgiev et al., 2010; Clifford et al., 2015).

With respect to cytokine targets, aspirin demonstrated binding energies of -61.64 kcal/mol and -55.66 kcal/mol for IL-1 and IL-6, respectively. These cytokines are key drivers of the inflammatory response, promoting leukocyte activation, fever, and acute-phase protein synthesis (Tanaka et al., 2014). Notably, all major HMEBV-derived compounds displayed stronger binding to IL-1 and IL-6 than aspirin. For instance, methyl stearate and 6-Octadecenoic acid, methyl ester showed binding energies of -75.30 and -75.29 kcal/mol to IL-1, and -68.47 and -69.04 kcal/mol to IL-6, respectively. These results suggest a high potential for downregulation of cytokine activity and subsequent suppression of inflammatory signaling.

The favorable binding profiles of these phytochemicals may be attributed to their structural characteristics, including long hydrophobic chains and functional groups capable of forming stable interactions within the active sites of target proteins. Importantly, the strong binding affinities to IL-6 by 9-Octadecenoic acid (Z)-, methyl ester (-72.47 kcal/mol) and to IL-1 by 9,12-Octadecadienoic acid (Z,Z) methyl ester (-74.65 kcal/mol) further emphasize the therapeutic promise of these compounds in conditions characterized by cytokine overexpression, such as rheumatoid arthritis and sepsis (Tanaka et al., 2014).

Although Heptasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethyl- showed comparatively lower affinities across all targets, it still exhibited moderate interaction values (e.g., -58.76 kcal/mol to FcγRI and -60.58 kcal/mol to IL-6), indicating a possible supportive or synergistic role in anti-inflammatory activity. This suggests that the overall therapeutic efficacy of HMEBV may be due to the combined or synergistic effects of its phytochemical constituents rather than the action of a single compound, consistent with the phytomedicinal paradigm (Newman & Cragg, 2020).

VI. Conclusion

The superior binding affinities of several HMEBV-derived compounds to FcγRs and pro-inflammatory cytokines, compared to aspirin, support the potential of Beta vulgaris as a source of novel immunomodulatory agents. These findings highlight the need for further in vivo and clinical investigations to validate the bioactivity, safety, and pharmacokinetic profiles of these phytochemicals in the context of inflammatory and autoimmune diseases.

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