

Frankincense Stem Bark and Resin Extract: Molecular Insights into Anti-Dyslipidemic and Neuroprotective Effects in Obesogenic Diet-Induced Impairment

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Abstract

This study compared the potencies of the resin (BRE), stem bark (BSE), and their combined diherbal extract (BSRE) against a standard scavenger. Phytochemical constituents were identified using Gas Chromatography-Mass Spectrometry (GC-MS), while the detected metabolites were docked against dopamine, and compared with a standard ligand. Among the extracts, BSRE demonstrated the most encouraging plateau and competitive potencies against the standard reductant, while the identified thirty-eight (38) volatile constituents in BSRE, with three dominant compounds accounting for 64.27%. Additionally, some metabolites exhibited the strongest binding affinities for dopamine, outperforming ascorbic acid, the reference agent. Moreover, in an acute study involving high-fat diet (HFD) fed 50 Wistar rats (25 males and 25 females), the study disclosed significantly ameliorated HFD-induced pathologies in the co-treated animals. Co-treated female rats further exhibited a more robust hormetic recovery, while males responded more effectively at higher doses, suggesting enzymatic/sex-specific/hormone-mediated responses. Histopathological assessments further confirmed BSRE's neuroprotective effects, particularly at higher doses in male brains but lower doses in females. Eight Key phytometabolites were established to contribute to the extract's potencies via docking trials, with their metabolic effects including decreased susceptibility of LDL to peroxidation and eventual neurological remediation. Overall, the potential of BSRE as a promising phyto-therapeutic agent for mitigating obesogenic-induced metabolic disorders was established, while further studies are warranted to evaluate the stability, shelf life, and clinical applicability of the eight key phytocompounds.

Keywords: *Boswellia dalzielii*, Frankincense, GC-MS, Plateau level, Neuroprotection, High-fat diet, Molecular Simulation, Neurotransmitters, and Castelli's index I.

Introduction

Obesity, generally driven by high-fat diets/meals (HFD), is a risk factor for dyslipidemia and neurodegenerative disorders due to its role in promoting oxidative stress and synaptic dysfunction in the brain of both males and females. These unbalanced diets are also known etiology to modulate neuroinflammatory processes, particularly involving dopamine, (Kang et al., 2023), serotonin, acetylcholine (Qi et al., 2020), gamma-aminobutyric acid, and myeloperoxidase (MPO) (Benson et al., 2018). Dopamine, a monoamine neurotransmitter, and myeloperoxidase (Lauretani et al., 2024) play essential roles in motor-control reasoning, motivation, reward, cognitive function, intellectual ability, and mood expressions (Ünlü et al., 2023). Hence, targeting MPO activities and dopamine levels may offer therapeutic potencies for treating neurological disorders, mostly characterized by oxidant-induced inflammation of lipids and other biomolecules (Siddiqui et al., 2023). Furthermore, chronic HFD consumption has been shown to impair the brain's reward system, correlating with reduced brain integrity (Onaolapo et al., 2023b). The damage to these cell membranes resulting from oxidative stress, also accounts for the pathogenesis of age-related neurodegenerative diseases (Chai et al., 2019) such as dementia (Abedi et al., 2023).

High-fat-related dysfunction remains a global neurological imbalance, posing significant health challenges in both male and female genders, especially in developed countries and urban societies (Moreno-Fernández et al., 2018). The World Health Organization (W.H.O.) even highlighted the broader implications of unhealthy diets, including those high in fats, sugars, and salts, which contribute to various hypercholesterolemia, neuroinflammation, and cognitive decline in the elderly (Sharma, 2021). In Nigeria, for instance, Dr. Temitope Farombi, a consultant neurologist at the University College Hospital, Ibadan, projected a significant rise in brain disorder cases by 2030 (Adegbite, 2025), while (Lizarbe et al., 2019) noted that rats exposed to diets rich in fat displayed symptoms of Schizophrenia, impacting memory, attention, and executive functions.

In recent years, the applicability of traditional medicine and modern research has revealed the therapeutic potential of many medicinal plants, particularly in regions where indigenous practices are mostly considered as first aid of treatment. One such endowment specie is *Boswellia dalzielii* (Hutch.), commonly known as frankincense or Turari oja in the Yoruba-speaking zones of Nigeria. Traditionally, it has been used for managing various ailments for millennium, including epilepsy (Medugu et al., 2020a), Parkinsonism and Alzheimer's disease (Rajabian et al., 2020), neurological (Moussaieff & Mechoulam, 2009) and psychiatric disorders (Calabrese et al., 2024). The stem bark and oleo-gum resin of this tree are valued in traditional medicine for their anti-inflammatory, analgesic, and antioxidant properties. While the plant is usually found across West Africa, particularly in the Sudanian, sub-Sahel zones of Mali, Burkina Faso, and northern Nigeria (Sabo et al., 2022), however rigorous scientific validations and the synergetic potential of the oleo-gum resin sometimes called myrrh and stem bark combination as generally applied by religious worshippers for centuries, have been sparse. Traditionally, *B. dalzielii* is popularly used via pyrolysis in Nigeria and other West African countries (Fasan et al., 2023), yet its neuroprotective mechanisms, particularly in high-fat diet-induced models of brain dysfunction, are not well understood and verified (Khaafi & Javadi, 2023). However, phytochemical screening of the ethanol extract of *B. dalzielii* stem bark has shown the presence of terpenoids in the form of saponins, flavonoids, tannins, and steroids. (Mamza et al., 2018), while the intraperitoneal median lethal dose score (LD50) of the plant stem bark in mice was 2592.3 mg/kg, hence indicating the stem bark extract is relatively safe (Medugu et al., 2020b), and with evidence of its antiepileptic agent in mice accounted by (Medugu et al., 2020c).

The discovery of Western drugs requires intensive research in order to identify candidates with viable therapeutics and minimal adverse effects. More specifically, molecular simulation has emerged as a supportive technique in this regard, enabling researchers to predict and analyze the pharmacokinetic properties (Absorption, Distribution, Metabolism, Excretion, and Toxicity) and molecular interactions between the suspected ligands and their bio-receptors, and in order to ascertain the high drug-likeness accuracy before eventual preclinical and clinical study. Simulation of GC-MS-identified compounds was hence conducted with a neuroreceptor, particularly dopamine, to evaluate their neurological drug likeness properties, and possibly corroborate the account with the pre-clinical animal studies. Consequently, this study sets out to evaluate the binding affinity of the identified volatiles with dopamine, determine the in-vitro plateau/scavenging abilities of the three extracts and to understudy and compare the anti-hyperlipidemic, neuroprotective, and antiperoxidative effects of the aqueous-alcoholic extract of *Boswellia dalzielii* stem bark and resin combination (BSRE) in the serum and brains of an adipose male and female animal model.

Materials and Methods

Chemicals and Reagents

Thiobarbituric acid (TBA), trichloroacetic acid (TCA), 5',5'-dithiobis-(2-nitrobenzoic acid) (DTNB), epinephrine, tetramethyl benzidine (TMB), ammonium molybdate, 2,3,5-triphenyl-1,3,4-triaza-2-azoniacyclopenta-1,4- diene chloride (TPTZ), oxidized Nicotinamide Adenine Dinucleotide (NAD), and Griess reagent were obtained from Sigma-Aldrich (St-Louis, MO, USA). While formalin, ethanol, dimethyl sulphoxide (DMSO), and hydrogen peroxide were obtained from Scharlau (Scharlau S.L., Spain). All other chemicals and reagents used for this study were of analytical grade and procured from standard commercial suppliers in Nigeria.

Collection of Plant Materials

The *Boswellia dalzielii* plant parts (leaves {BDL}, stem bark {BDS}, and resin {BDR}) were collected from their habitat at Gwash II, Jos LGA, Plateau state, on LAT: 9.964 44, Long: 8.96288, Jos, and authenticated by Dr. T.K. Odewo, a taxonomist at the Herbarium unit, Federal Research Institute of Nigeria (FRIN), Ibadan. The plant material was eventually tagged with voucher no FRIN-11361 and preserved at the herbarium.

Preparation of Plant Materials and Herbal Formulation

The freshly harvested plant parts, BDS, and BDR were subjected to air drying for 70 days until constant weight was attained. They were then pulverized at the ISO-registered Laboratory of the Nigeria Natural Medicine Development Agency, according to the method described by (Handa et al. (2008) and (Sulaiman et al. (2011), with a slight modification. Each of the pulverized samples (750g) was extracted for five days with 2000 mL of aqueous ethanol solvent (30:70 v/v) and eventually freeze-dried to obtain crude BDS and BDR extracts. The yields of the formulation BDSR (a mix of BDR and BDS at an 80:20 ratio by weight) aqueous ethanolic extract (BSRE), BDS aqueous ethanolic extract (BSE), and that of BDR aqueous ethanolic extract (BRE) were 24.7%, 23.93% and 7.94% respectively. The final BSRE, BSE, and BRE were immediately stored in an air-tight amber bottle and kept in a freezer at around -4°C until further use. It is worthwhile noting that extracting the oleo-gum resin using a Soxhlet extractor was not feasible due to the sticky nature of the terpenes, which include α -pinene, limonene, essential oils, gum, and polysaccharides (Niphadkar et al., 2017). Hence, Soxhlet extraction, rotary evaporation, and freeze

drying were employed for the dried stem bark, and the formulation, while maceration with intermittent shaking, sieving with 50-micron muslin cloth, filtration using Whatman 150mm filter paper, and eventual freeze drying were used only for the resin.

Phytochemical screening

The BSRE was subjected to Gas Chromatography-Mass Spectrometry (GC-MS) analysis to identify the bioactive volatile essential oils (Mertens et al., 2009) at the Nigerian Institute of Medical Research (NIMR) Laboratory, Yaba, Lagos State. This sample was reconstituted with distilled water at a concentration of one (1) microgram/ml, and one microliter of the resulting solution was injected into the GC-MS inlet, which was eventually ionized into fragments of different spectra, transduced by the pressurized helium gas at 40-80 pounds per square inch (psi). The energized aqueous fraction flows through the column, and identifiable compounds were separated by their relative ionization potentials. Eluting from the column were spectra, detected according to their mass-to-charge proportionality. Each spectrum was eventually compared with a reference library/database resource, MassHunter/Library\National Institute of Standards and Technology (NIST) 14L (Yan et al., 2020), and thirty-eight (38) phyto-constituents, each with a peak, were identified across fourteen retention times (in minutes) as listed in Table 2.

In-silico docking/ADMET/Glide Screening

The volatile phytoconstituents identified from the GC-MS analysis of *Boswellia dalzielii* stem bark and resin extract combination (BSRE) were subjected to in-silico molecular docking to evaluate their potential interactions with dopamine, a key neurochemical marker implicated in high-fat diet (HFD)-related neurodegenerative impairments. The three-dimensional structures of all identified compounds were retrieved from the PubChem database in Structure Data File (SDF) format. These compounds were screened for drug-likeness and oral bioavailability using Lipinski's Rule of Five (Ro5), which includes the following criteria: (i) molecular weight less than 500 Daltons, (ii) log P (octanol–water partition coefficient) less than 5, (iii) no more than 5 hydrogen bond donors, and (iv) no more than 10 hydrogen bond acceptors. Additional ADMET-related properties considered are total solvent-accessible surface area (acceptable range: 300–1000 Square Angstroms {Å²}), predicted log P (QPlogPo/w) (recommended hydrophilic -2 to 5.0 lipophilic), blood-brain barrier partition coefficient (recommended: -3 to 1.2), aqueous solubility (mol/dm³; acceptable: -6.5 to 0.5), and human oral absorption percentage (ideally approaching 100%). Advanced molecular docking, pharmacodynamic, and pharmacokinetic assessments of the GC-MS identified compounds towards dopamine were further conducted using the Schrodinger Maestro Suite 2024 (version 13.9), through Glide docking, Molecular Mechanics Generalized Born Surface Area (MMGBSA), and ADMET prediction tools (Ramya et al., 2024). This integrated computational strategy aimed to reduce the risk of preclinical failure by prioritizing phytochemicals with favorable drug-like properties and neuroprotective potential as described by (Shrestha et al., 2022) and (Karami et al., 2022).

In-Vitro Scavenging Properties of the Extracts

The in-vitro antioxidant activities of the three extracts were screened and compared using a iron 11 sulphate (Fe²⁺) chelating assay based on the Fe²⁺–ferrozine spectrophotometric method described by (Butkutė et al., 2018), while the concentration–response data were subjected to nonlinear regression using the four-parameter logistic model in GraphPad Prism version 10.4. The IC₅₀ values and plateau levels were eventually determined from the dose–response curves from

nonlinear regression option and based on the established IC₅₀ and plateau results, BSRE was selected for subsequent evaluation in high-fat-diet (HFD)-induced brain steatosis, dyslipidaemia, and neurological derangements in male and female Wistar rats.

Acquisition of Experimental Animals and Chow

Male and female Wistar rats were purchased from the Nigeria College of Natural Medicine, Nigeria Natural Medicine Development Agency, Federal Ministry of Innovation, Science and Technology (FMIST), while the high-fat chow of 48,8% lard composition and normal diet were procured from Funsab Enterprises, a producer and supplier of agro and livestock raw materials in Lagos, Nigeria, with their composition details listed in Table 1.

Table 1: Composition of High-Fat and Normal Chow

Normal Diet	High Fat Diet
Lard 0	Lard 48.8
Wheat offal 48.8	Wheat offal 0
Maize 10	Maize 10
Calcium 4	Calcium 4
Groundnut cake 6	Groundnut cake 6
Soya bean meal 10	Soya bean meal 10
Additives 1.2	Additives 1.2
Palm kernel cake 20	Palm kernel cake 20

Animal grouping

After the acquisition, rats were separated based on their gender into different cages and housed at the vivarium of the Department of Biochemistry, Federal University of Technology Akure, Nigeria for acclimatization under standard conditions (25 ± 3 °C, 60-70% relative humidity under 12:12hrs light/dark cycle) for two weeks, during which they were fed with normal rat chow and water ad libitum. The experimental rats were eventually grouped by gender (25 females and 25 males) into two sets as follows:

Set one (Male Rats):

Group 1: Male rats on normal rat chow.

Group 2: Male rats on a high-fat diet (HFD).

Group 3: Male rats co-treated with 125mg/kg/bodyweight of BSRE and HFD.

Group 4: Male rats co-treated with 150mg/kg/bodyweight of BSRE and HFD.

Group 5: Male rats co-treated with 200mg/kg/bodyweight of BSRE and HFD

Set two (Female Rats):

Group 1: Female rats on normal rat chow.

Group 2: Female rats on a high-fat diet (HFD).

Group 3: Female rats co-treated with 125mg/kg/bodyweight of BSRE and HFD.

Group 4: Female rats co-treated with 150mg/kg/bodyweight of BSRE and HFD.

Group 5: Female rats co-treated with 200mg/kg/bodyweight of BSRE and HFD

Sacrifice of experimental rats and Brain Harvest

Animals were sacrificed by cervical dislocation after 24 hours of fasting following the last co-treatment, brains harvested, blood collected into serum bottles, and the weights of the harvested brains measured, recorded, compared, statistically analyzed, and the pathohistological examination was subsequently done microscopically (Rospond et al., 2022).

Biochemical evaluation

In-vivo Redox Status and Lipid Profile

Brain oxidative/redox status was assessed by determining glutathione peroxidase (GPx), catalase (CAT) activity, reduced glutathione (GSH) concentration, and lipid peroxidation as malondialdehyde (MDA) in brain homogenates as reported by (Onalapo et al., 2023a), (Akinmoladun et al., 2021), and (Obradovic et al., 2015) with little modification. While serum lipid profile was assessed by determining the Castelli Risk Index as a lipid-associated cardiovascular risk factor, following the account of (Obradovic et al., 2015).

Neurobehavioral Markers Test

Dopamine and Myeloperoxidase were also estimated using the modified methods of (Ojo et al., 2023), (Nahla et al., 2024) and (Kaur et al., 2023).

Histopathology

Brain sections were immediately examined for possible changes in architecture, neuronal integrity, and signs of inflammation using eosin (H&E) staining (mag x200).

Statistical Analysis

The quantitative results with triplicate data were represented as mean $\pm$ standard error of the mean (SEM), analyzed using Graph Pad prism version 10.4 with One-way Anova, and considered significant at $p < 0.05$ under Tukey's multiple comparison test, while the correlation between the males' and females' data were analyzed with Two-way grouped Anova analysis. The IC₅₀ and plateau levels were eventually quantified using non-linear regression analysis via a four-parameter option (log inhibitor vs. response, variable slope).

Results

In-vitro scavenging capacities of BSE, BRE, and the combination BSRE

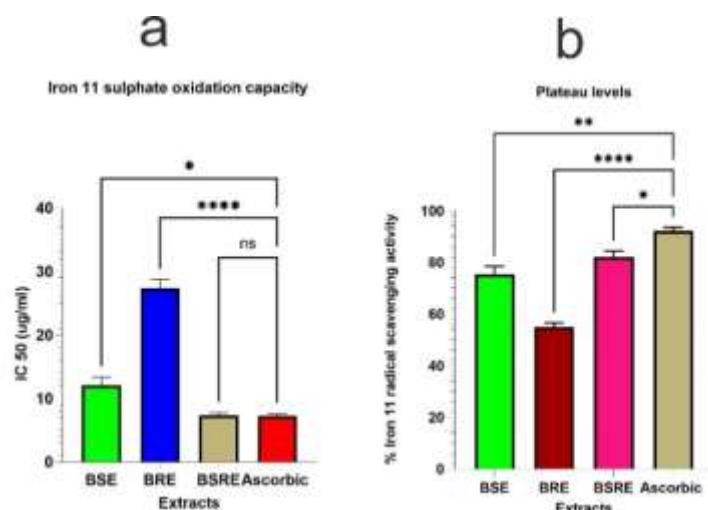


Figure 1: Half maximal inhibitory concentration (IC₅₀, µg/ml) and plateau activities of *Boswellia dalzielii* resin (BRE), stem bark (BSE), and the combined extract (BSRE) on Iron (11) sulphate chelating assay along with ascorbic acid as a reference agent.

Keys:

BD – *Boswellia dalzielii* (Hutch)

BSRE – Aqueous ethanolic extract of combined BD stem bark and resin (80:20 w/w)

BRE - *Boswellia dalzielii* resin aqueous ethanolic extract

BSE - *Boswellia dalzielii* stem bark aqueous ethanolic extract

Data presented as mean ± SEM of n=5.

ns – no significant difference as compared to control;

**** – very highly significance ($p < 0.05$) as compared to control.

HFD – High-Fat Diet

bwt – body weight

Figure 1 shows the half maximal inhibitory concentrations (IC₅₀, expressed in µg/mL) and the plateau activities of BRE, BSE, and BSRE on Iron 11 chelating assay along with ascorbic acid as the reference agent. Among the extracts, BSRE demonstrated the lowest IC₅₀ indicating enhanced antioxidant potency likely due to a synergistic interaction between the resin and stem bark constituents. This synergism, supported by the phytochemical composition as depicted in Table 2, especially the top eight phytocompounds, likely resulting in greater chelating capacity of BSRE compared to the individual extracts. Furthermore, the plateau activities revealed that BSRE possessed superior reductive potential, approaching the efficacy of the reference ascorbic acid more closely than BRE and BSE. Collectively, this suggests that BSRE holds significant promise for mitigating pathological redox imbalances in pharmacognostic applications.

Effect of BSRE on Brain Weight of assaulted and co-treated rats

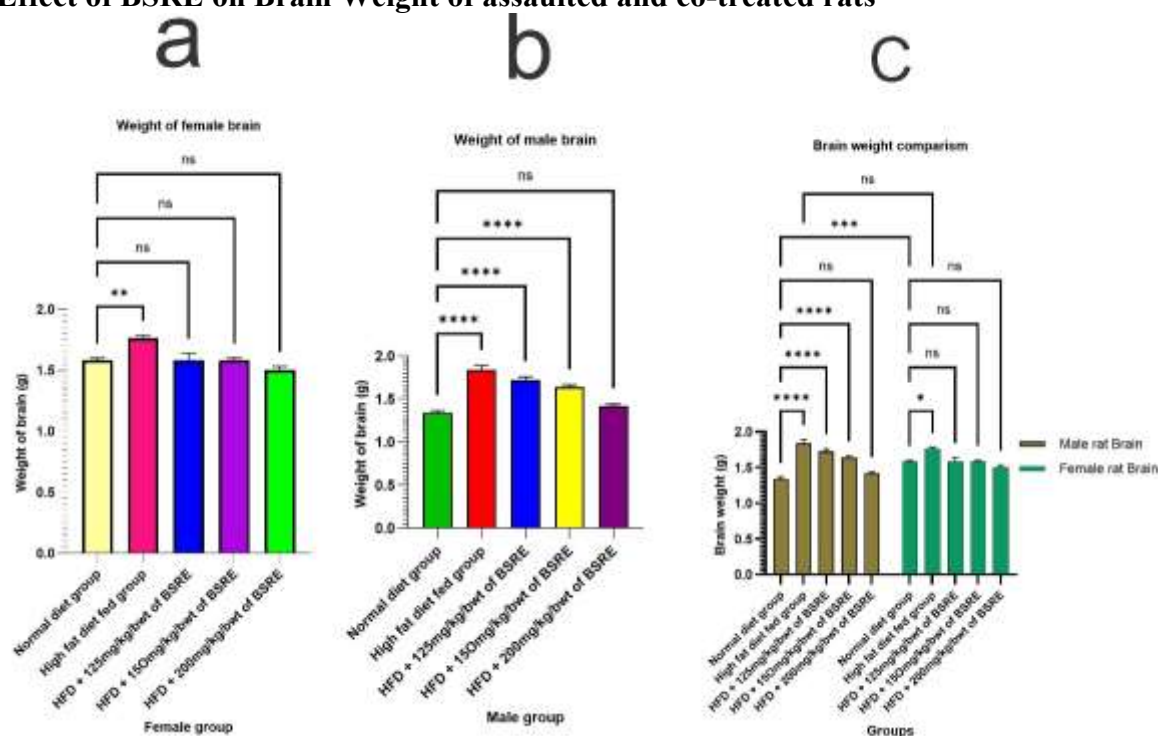


Figure 2: Brain weights of assaulted and co-treated rats

Figures 2a, 2b, and 2c illustrate the brain weights of BSRE co-treated female and male rats, as well as both genders compared, over a 60-day exposure period. High-fat diet (HFD) administration led to a significant increase in brain weight ($p < 0.0001$) in both female and male rats compared to those on a normal diet, suggesting brain steatosis (Van Ginneken et al., 2017). Though, the difference was not significant ($p=0.8269$) when comparing both assaulted genders fed HFD after the acute period, as shown in figure 3c, suggesting similarities in brain steatosis. However, BSRE co-treatment elicited a dose-dependent recovery in male brain weight, approaching normal values compared to females that produced a non-dose-dependent improvement at all administered doses, with no significant difference in the female brain weight relative to normal diet-fed females. This implies a potentially enhanced lower extract efficacy in females at $p>0.9999$, $p>0.9999$ and $p=0.3088$ to near normal, possibly mediated by female hormonal modulation on blood-brain barrier permeability (Hewagalamulage et al., 2016). Additionally, when comparing the brain weights between sexes on a normal diet (Figure 3C) after the assaulted period, female rats showed significantly higher brain weights than males. In conclusion, co-treated female rats tend to recover faster than males, with only the dosage at 200mg/kg/bwt, demonstrating greater potency in the brain weight of the male co-treated group. These findings underscore the potential of BSRE in mitigating diet-induced brain weight gain or brain steatosis (Silverberg, 2004), as also previously reported by (Van Ginneken et al., 2017).

Effect of BSRE on Neuro-inflammation Markers of assaulted and co-treated rats

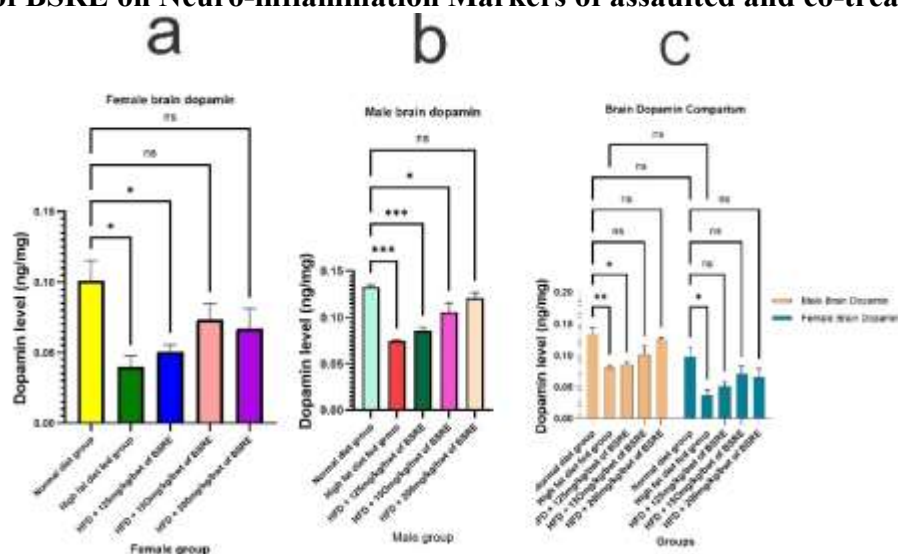


Figure 3: Brain Dopamine activity in assaulted and co-treated animals

Figures 3a, 3b, and 3c present brain dopamine levels in BSRE co-treated male and female rats subjected to a high-fat diet (HFD), along with a comparison between the genders. The results indicated that dopamine levels were significantly reduced ($p < 0.0101$) in both high-fat diet (HFD) fed male and female groups compared to those fed a normal diet. However, this decrease was significantly ameliorated in a dose-dependent manner to near normal in the male co-treated group. In contrast, the female co-treated group exhibited no significant difference in dopamine levels at 150 and 200 mg/kg/bwt compared to the normal diet-fed animals. As further depicted in Figure 4c, there was no significant difference in dopamine levels between genders fed a normal or high-fat diet after the acute period. This pattern suggests that normal and HFD induce similar neurochemical impairments, due to brain barrier and redox adaptability in both sexes (Neuman et al., 2022). After co-treatment, males further displayed a more pronounced difference at 125mg/kg/bwt, while females exhibited near-normal levels at the same dose (Figure 4C refers). Consequently, BSRE's restorative effect is dose-dependent in males than in females at the same doses, indicating sex-dependent susceptibility and therapeutic responsiveness.

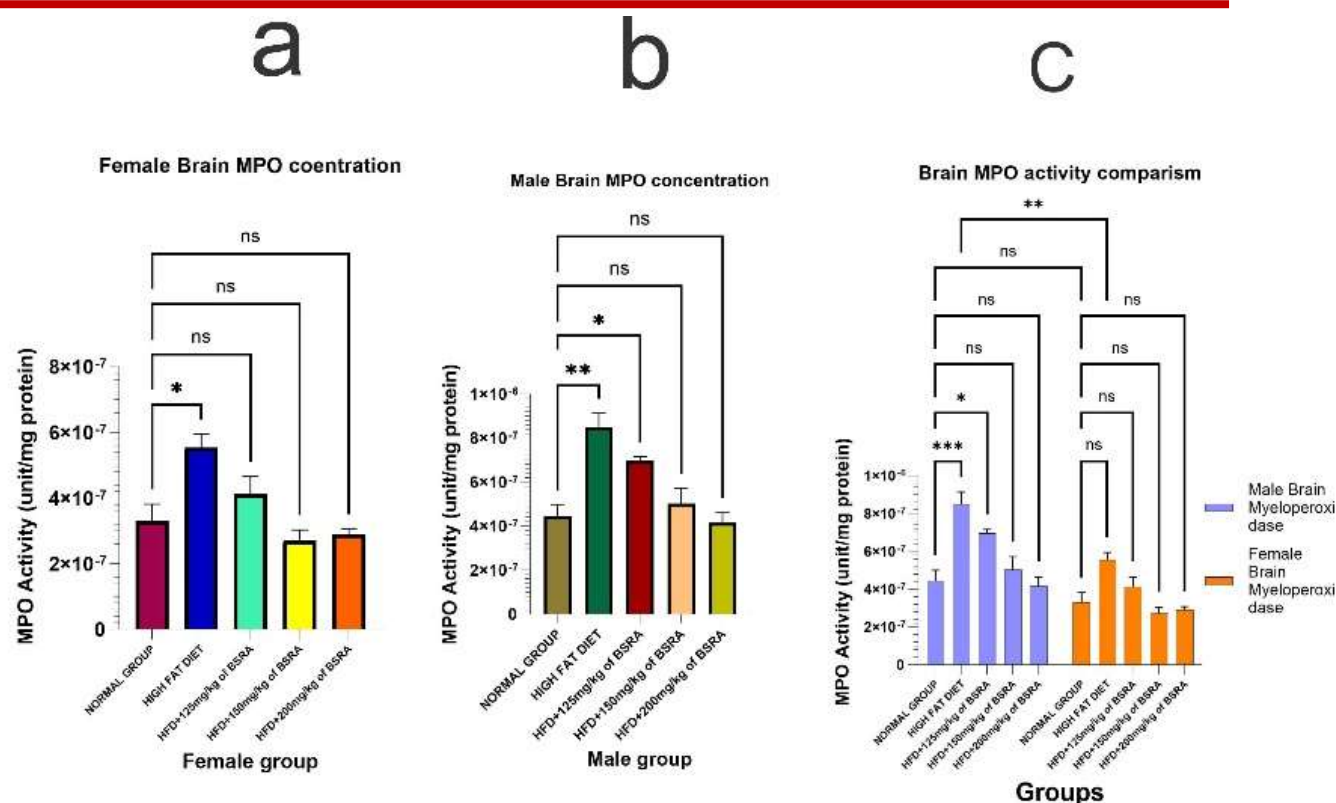


Figure 4: Brain Myeloperoxidase activity in assaulted and co-treated animals

Figures 4a, 4b, and 4c disclose the Brain myeloperoxidase (MPO) activity in HFD-fed and BSRE co-treated male and female rats, along with a gender comparison. The results indicated that myeloperoxidase activity was significantly increased in both HFD-fed female and male rats compared to the normal diet-fed groups. However, this increase was dose-independently ameliorated and normalized in the co-treated female rats, while it was dose-dependently attenuated in male counterparts co-treated with 125, 150, and 200 mg/kg body weight. When comparing MPO activity between male and female rats (Figure 4C), the results demonstrated that MPO activity was significantly higher in male rats than in females fed the same high-fat diet, with no significant differences observed in the normal diet-fed male and female rats after the acute period. In conclusion, male animals appeared more susceptible to the effects of the high-fat diet on brain MPO activity than females, with the latter recovering more quickly.

Effect of BSRE on Anti-oxidative Status of assaulted and co-treated rats

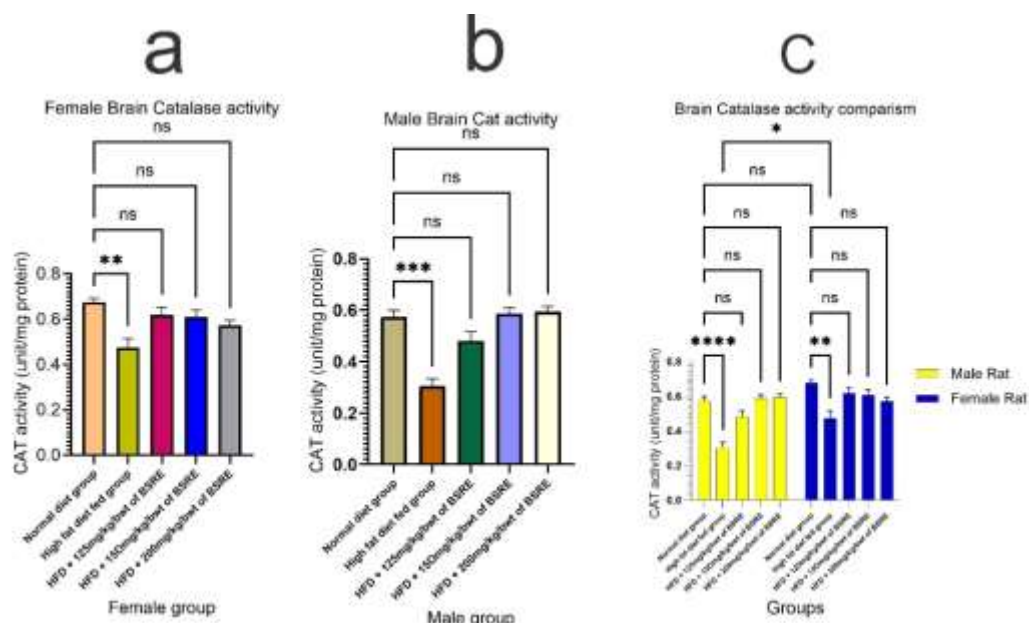


Figure 5: Brain Catalase activity in assaulted and co-treated rats

Figures 5a, 5b, and 5c illustrate the brain catalase levels in assaulted, BSRE co-treated female and male rats, and both sexes compared. The results indicated a significant decrease ($p < 0.05$) in brain catalase levels of both male and female rats fed a high-fat diet (HFD) compared to those on a normal diet. This decrease was significantly ameliorated in a dose-independent manner in the male and female groups co-treated with varying doses of the extract, as all the co-treated groups disclosed no significant differences from the animals on a normal diet. Furthermore, the comparison of brain catalase levels presented in Figure 5c revealed no significant differences between normal diet-fed male and female animals after the acute period. On the contrary, the assaulted male and female animals demonstrated a significant difference when compared, indicating that the brain catalase activity of the assaulted female animals is higher and hence more resilient to the stressor than the male animals, likely due to hormonal variations. These findings thus suggested that estrogen (Zhang et al., 2002) progesterone, oxytocin, and cortisol (Atsarina et al., 2024) responses play a crucial role in enhancing adaptability in females compared to males, with lower levels of these hormones (Hewagalamulage et al., 2016).

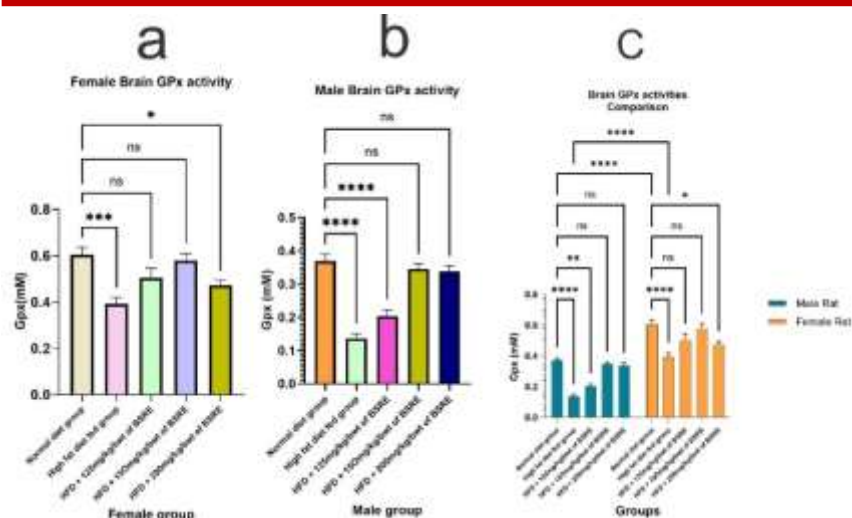


Figure 6: Brain Glutathione peroxidase activity in assaulted and co-treated rats

Figures 6a, 6b, and 6c unveil the brain glutathione peroxidase (Gpx) activity in assaulted and BSRE co-treated male, female rats, and gender comparison, respectively. The results showed a drastic decrease ($p < 0.05$) in the brain Gpx activities in both high-fat diet-fed female and male rats compared to the normal diet-fed group, followed by a gradual increase in Gpx activities in male rats co-treated with the doses of the extract. In contrast, no significant difference was observed in the brain Gpx activity of female rats co-treated with the extract at 125 and 150 but not at 200 mg/kg bwt, suggesting a hormetic recovery effect to near normal (Scuto et al., 2024). Further comparison revealed that Gpx activities in female rats, both on normal and high-fat diets, were significantly higher than those of their male counterparts on the same diets after the study duration. In conclusion, female co-treated rats have better Gpx activity and tend to recover more quickly to near-normal levels compared to their male counterparts.

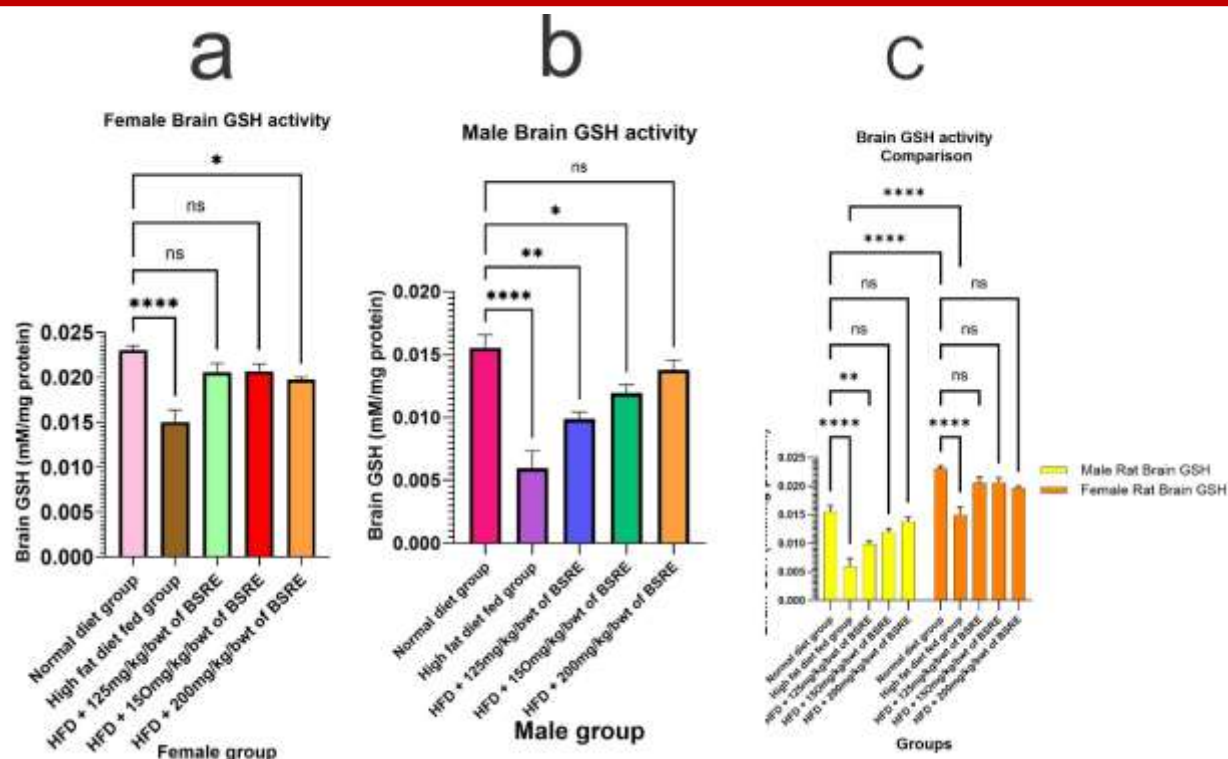


Figure 7: Brain Glutathione levels in assaulted and co-treated rats

Figures 7a, 7b, and 7c illustrate the levels of reduced glutathione (GSH) in the brains of assaulted, BSRE co-treated male and female rats, along with a gender comparison. The results demonstrated a significant decrease ($p < 0.05$) in brain GSH levels in both high-fat diet (HFD)-fed male and female rats compared to those on a normal diet. This decrease was, however, significantly ameliorated in males to near normal in a dose-dependent manner, while hormetic recovery was further noted for females at 125 and 150mg/kg/bwt, denoting faster recuperation in the brain of the latter. More importantly, the female group administered 200 mg/kg bwt BSRE showed a significant decline in GSH activity compared to those on normal chow, indicating that the highest dose might have exceeded the extract's beneficial range and produced a biphasic or hormetic response in the brain, as also established by (Skaperda et al., 2022). Additionally, the gender comparison revealed significant GSH activity ($p < 0.05$) in female rats compared to male animals in both normal and high-fat diet-fed groups. In conclusion, the extract demonstrated hormetic efficacy in female brain GSH levels compared to males, harmonizing with the findings of (Nazari & Moosavi, 2022) and (Scuto et al., 2024).

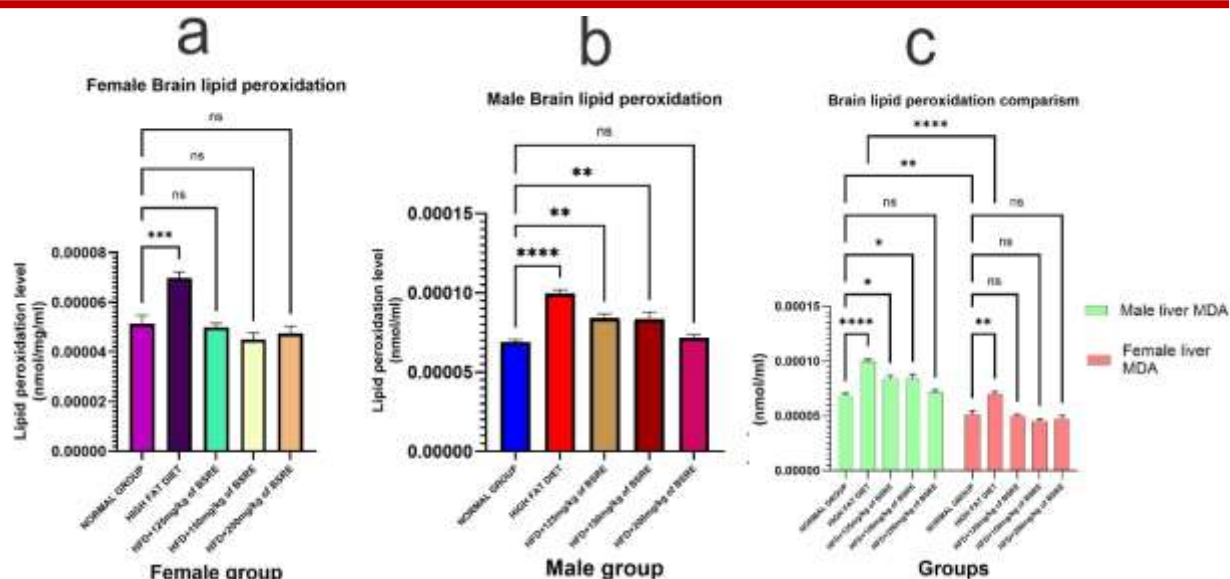


Figure 8: Brain Lipid peroxidation (MDA) levels in assaulted and co-treated rats

Figures 8a, 8b, and 8c reveal the brain MDA levels of assaulted, BSRE co-treated male, female rats, and the gender comparison, respectively. The results disclosed a significant increase in the brain MDA levels of both high-fat diet-fed female and male rats compared to those on a normal chow at $p \leq 0.0003$. In the co-treated male group, brain MDA levels were significantly attenuated dose-dependently to near normal. In contrast, female rats further responded to varying doses (125, 150, and 200 mg/kg body weight) of the extract with no differences, as groups 3 to 5 in females recovered to near normal levels. These responses may be attributed to the immune-enhancing abilities of female hormones on the blood-brain barrier, as reported by (Bake et al., 2014) and (Nazari & Moosavi, 2022). Furthermore, gender comparisons, as shown in Figure 8c, revealed that MDA levels in female rats, both in normal and high-fat diet groups, were significantly lower than those in male rats. This suggested that the males are more allergic to the stressor, while the females tend to be resilient and recover more quickly from the co-treatment regimen than the males.

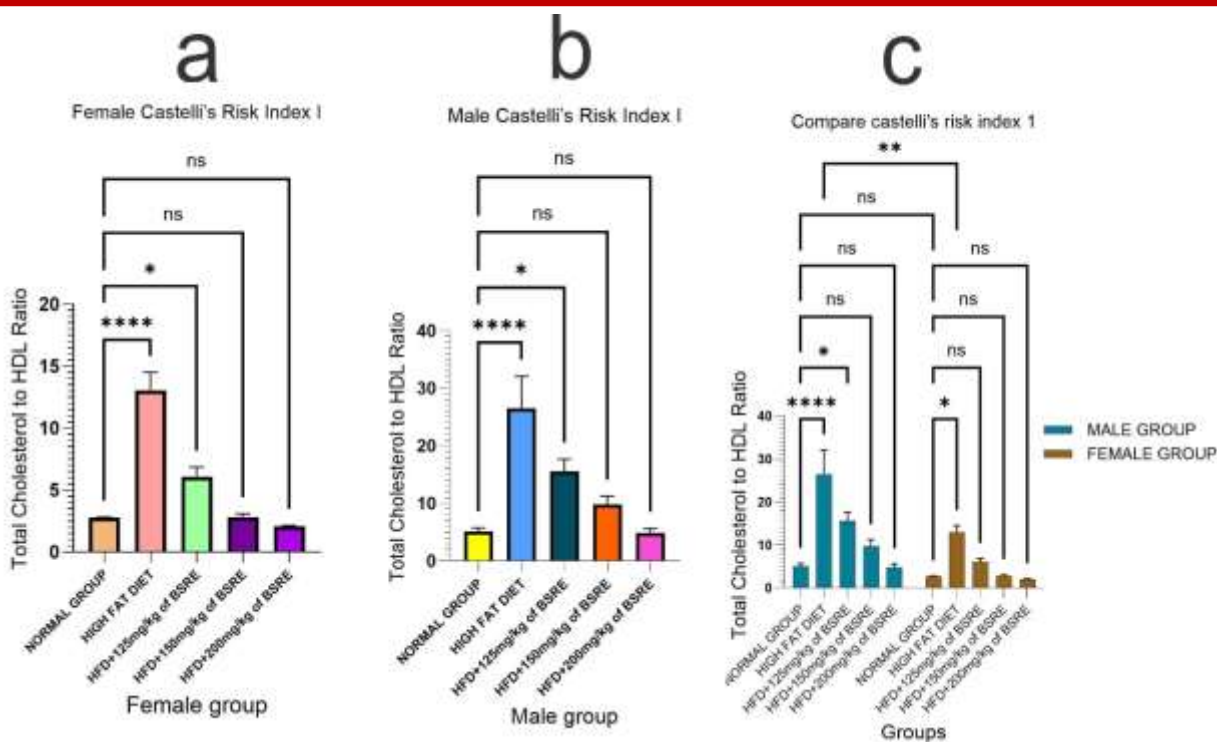


Figure 9: Castelli's Risk index 1 of assaulted and co-treated rats

Figures 9a, 9b, and 9c show Castelli's Risk Index I (Total Cholesterol to HDL ratio) of assaulted (high-fat diet fed) and BSRE co-treated female and male rats, alongside their comparisons between the groups. In both sexes, the high-fat diet (HFD)- fed groups showed a significant increase in the serum Castelli's Risk Index 1 compared to the normal animals ($p < 0.05$), indicating a higher cardiovascular risk, as also reported by Yıldız et al. Co-treatment with 125 mg/kg body weight of BSRE significantly reduced the index compared to HFD alone, while both 150 mg/kg and 200 mg/kg BSRE co-treatments further brought the index to normal levels, suggesting a dose-dependent protective effect in both co-treated female and male rats. Comparing the animals as shown in Figure 9C, the males on a high-fat diet demonstrated significantly higher Castelli's Risk Index I values than females on the same diet, indicating that male rats are more susceptible to HFD-induced dyslipidemia and cardiovascular risk than females. The co-treated male group also showed a notable difference in the risk index at 125 mg/kg body weight compared to the normal diet group but revealed no significant difference at higher doses of BSRE (150 and 200 mg/kg body weight), contrary to females, that exhibited full remediation to near-normal levels at all doses (figure 9c refers). Overall, the data demonstrated that a high-fat diet significantly elevates Castelli's Risk Index I in both sexes, with males being more adversely affected, which could be informative for gender-specific studies in managing diet-induced dyslipidemia and cardiovascular risk.

Table 2: GC-MS result of *Boswellia dalzielii* frankincense+resin aqueous ethanolic extract (BSRE)

Peak number	Retention time (mins)	Peak height	Abundance/Area	Percent age of total	Detected Phytochemicals as referenced by the NIST Library	Reference
1.	3.556	261015.000	1701765.000	0.900 %	(1) 1,3,5-Cycloheptatriene, 3,7,7-trimethyl- (2) O- O-Cymene (3) Benzene, 1-methyl-3-(1-methylethyl)-	(1) 15258.000 (2) 15140.000 (3) 15244.000
2.	5.016	869303.000	2352395.000	1.244 %	(1) Bicyclo [3.1.0] hexan-3-ol, 4-methylene-1-(1-methylethyl)-, [1S-(1.alpha.,3.beta.,5.alpha.)]- (2) Bicyclo [3.1.1] heptan-3-ol, 6,6-dimethyl-2-methylene-, [1S-(1.alpha.,3.alpha.,5.alpha.)]-	(1) 26167.000 (2) 26159.000 (3) 26156.000
3.	5.079	1481007.000	5664232.000	2.995 %	(1) Trans-Verbenol (2) p-Mentha-1(7),8-dien-2-ol (3) Trans-p-mentha-1(7),8-dien-2-ol	(1) 25837.000 (2) 25900.000 (3) 25934.000
4.	5.525	4287220.000	11541828.000	6.104 %	(1) Verbenyl ethyl ether (2) Ethanone, 2-(4-	(1) 47888.000

					morpholinyl)- 1-phenyl	(2) 6955 7.000
					(3) Trans-3- Caren-2-ol	(3) 2585 8.000
5.	5.742	426039.0 00	1835 831.0 00	0.971 %	(1) 1,3-trans,5- cis-Octatriene	(1) 5553. 000
					(2) Cyclopentane, 1-ethenyl-3- methylene-	(2) 5603. 000
					(3) Benzyl alcohol	(3) 5468. 000
6.	5.914	2202174. 000	5836 765.0 00	3.087 %	(1) Bicyclo [3.1.1] hept-3- en-2-one, 4,6,6- trimethyl-, (1S)-	(1) 2459 7.000
						(2) 2456 6.000
						(3) 2459 5.000
7.	13.461	1849424. 000	3006 765.0 00	1.590 %	(1) 1,5- Cyclooctadien e, 1,5- dimethyl-	(1) 1614 2.000
					(2) (R,1E,5E,9E)- 1,5,9- Trimethyl-12- (prop-1-en-2- yl) cyclotetradeca -1,5,9-triene	(2) 1330 49.00 0
					(3) 5,5-Dimethyl- 1-vinylbicyclo [2.1.1] hexane	(3) 1618 8.000
8.	14.915	6204057. 000	13253 613.00 0	7.009 %	(1) 3E,7E,11E)-1- Isopropyl- 4,8,12- trimethylcyclo tetradeca- 3,7,11-trienol	(1) 1502 41.00 0
					(2) 1,5- Cyclooctadien e, 1,5- dimethyl-	(2) 1614 2.000
					(3) Camphene	(3) 1603 8.000

9.	15.075	39317013 .000	12153 4473.0 00	64.270 %	(1) Isopropyl- 1,5,9- trimethyl-15- oxabicyclo [10.2.1] pentadeca- 5,9-dien-2-ol (2) (1S,2R,5E,9E, 12R)-12- Isopropyl- 1,5,9- trimethyl-15- oxabicyclo [10.2.1] pentadeca- 5,9-dien-2-ol (3) Benzaldehyd, 4-(2- chlorobenzylo xy)-3,5- dimethoxy-	(1) 1656 50.00 0 (2) 1656 57.00 0 (3) 1649 31.00 0
10.	15.493	1282540. 000	3492 933.0 00	1.847 %	(1) 2,4-Dimethyl- 3-nitrobicyclo [3.2.1] octan- 8-one (2) 1,2- Dipropylcyclo propene (3) Cyclohexane, 1,3-dimethyl- 2-methylene-, cis	(1) 6233 9.000 (2) 1086 3.000 (3) 1092 9.000
11.	15.887	781345.0 00	192908 2.000	1.020 %	(1) 1-methyl-4- (prop-1-en-2- yl)-7- oxabicyclo [4.1.0] heptan- 2-one (2) Isopulegol (3) Cyclohexanon e, 4-ethenyl-	(1) 3637 1.000 (2) 2746 1.000 (3) 1071 1.000
12.	15.979	5474191. 000	12759 967.00 0	6.748 %	(1) 1-Isopropyl- 5,9,13- trimethyl- 4,16- dioxatricyclo[	(1) 1807 20.00 0

					11.2.1.03,5]he	(2) 7075
					xadec-8-en-	4.000
					12-ol	(3) 5986
					(2) Caparratriene	0.000
					(3) 7-Tetradecyne	
13.	16.013	1707072	2779	1.470	(1) Cyclopentanol	(1) 1806
			523	%	, 1-(1-methylene-2-propenyl)-	6.000
					(2) 2-Methyl-3-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-oxetane	(2) 8579
					(3) 4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)-	4.000
					(1) 7-Oxabicyclo[4.1.0]heptane, 1,5-dimethyl-	(3) 1656
14.	17.358	356768.00	1410	0.746	(1) 7-Oxabicyclo[4.1.0]heptane, 1,5-dimethyl-	(1) 1172
			011.00	%	(2) 4-Cyclohexylidene-n-butanol	1.000
					(3) Phytol	(2) 2758
						9.000
						(3) 1558
						49.00
						0

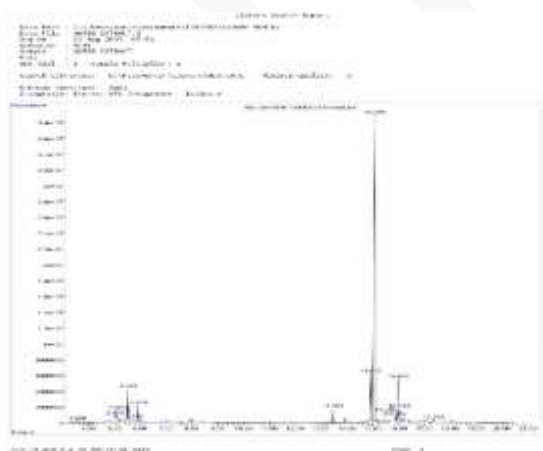


Figure 11: GC-MS Chromatogram of the aqueous ethanolic extract of BSRE

The GC-MS analysis of the water fraction of *Boswellia dalzielii* stem bark and resin extract (BSRE) is presented in Table 2 and Figure 11. The chromatographic profile revealed fourteen retention times (additional data available upon request), each associated with different mass spectra and abundance of various metabolites. In total, thirty-eight (38) phytochemicals were identified through spectral matching with the Mass Hunter/LibraryNIST14.L database. Among the detected compounds, the most abundant constituents are Isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol, (1S,2R,5E,9E,12R)-12-Isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol, and Benzaldehyde, 4-(2-chlorobenzoyloxy)-3,5-dimethoxy- with the highest peak area (64.270%), retention time of 15.075 minutes, and reference IDs 165650, 165657, and 164931 respectively. Additionally, prominent first-runner peaks (7.009%) at 14.915 minutes correspond to (3E,7E,11E)-1-Isopropyl-4,8,12-trimethylcyclotetradeca-3,7,11-trienol, 1,5-Cyclooctadiene, 1,5-dimethyl-, and Camphene. Conversely, the least abundant compounds, identified at a retention time of 17.358 minutes, include 7-Oxabicyclo [4.1.0] heptane, 1,5-dimethyl-, 4-Cyclohexylidene-n-butanol, and Phytol. Collectively, the identification of these thirty-eight phytoconstituents may underlie the observed pharmacological properties of the extract, as previously reported by (Salisu et al., 2018), (Yakubu et al., 2020), and (Medugu et al., 2020b).

Table 3: Molecular docking results of the GC-MS Identified Phytochemicals and Dopamine, along with Ascorbic acid as reference

No	COMPOUNDS' PUBCHEM CID/IUPAC NAME	Energy (kcal/mol)	Docking score	Glide gscore	Glide ligand efficiency	Glide energy (kcal/mol)
1	543945/2,4-Dimethyl-3-nitrobicyclo [3.2.1] octan-8-one	19.174	-3.359	-3.359	-0.240	-8.654
2	576906/Trans-3-Carene-2-ol	15.928	-3.309	-3.309	-0.301	-7.618
3	543953/Cyclohexanone, 4-ethenyl-	-4.455	-3.271	-3.271	-0.363	-7.083
4	564260/Bicyclo [3.1.0] hexan-3-ol, 4-methylene-1-(1-methylethyl)-, [1S-(1.alpha.,3.alpha.,5.alpha.)]-	17.092	-3.232	-3.232	-0.294	-6.275
5	244/Benzyl alcohol	10.262	-3.214	-3.214	-0.402	-6.503
6	102667/Bicyclo [3.1.1] heptan-3-ol, 6,6-dimethyl-2-methylene-, [1S-(1.alpha.,3.alpha.,5.alpha.)]-	33.476	-3.171	-3.171	-0.288	-6.337

7	89664/Trans-Verbeno	27.317	-3.146	-3.146	-0.286	-6.012
8	537752/7-Oxabicyclo [4.1.0] heptane, 1,5- dimethyl-	14.196	-3.033	-3.033	-0.337	-5.596
9	92874/Bicyclo [3.1.1] hept-3-en-2-one, 4,6,6- trimethyl-, (1S)-	33.462	-2.956	-2.956	-0.269	-5.495
10	10703/O- Cymene	12.881	-2.660	-2.660	-0.266	-5.459
11	10812/Benzene, 1- methyl-3-(1- methylethyl	9.634	-2.651	-2.651	-0.265	-6.022
12	576718/1,3,5- Cycloheptatriene, 3,7,7-trimethyl-	9.037	-2.628	-2.628	-0.263	-5.841
13	6428442/Trans-p- mentha-1(7),8-dien-2- ol	5.882	-2.575	-2.575	-0.234	-7.043
14	21122289/Cyclohexane , 1,3-dimethyl-2- methylene-, cis	6.083	-2.572	-2.572	-0.286	-5.620
15	170833/Isopulegol	9.839	-2.572	-2.572	-0.234	-7.284
16	5365758/1,5- Cyclooctadiene, 1,5- dimethyl-	7.081	-2.544	-2.544	-0.254	-5.822
17	6616/Camphene	31.974	-2.543	-2.543	-0.254	-5.333
18	100031/1-methyl-4- (prop-1-en-2-yl)-7- oxabicyclo [4.1.0] heptan-2-one	7.088	-2.539	-2.539	-0.212	-6.913
	Standard control	0.046	-2.440	-2.440	-0.203	-8.334
	54670067/Ascorbic Acid					
19	9904641/(1S,2R,5E,9E, 12R)-12-Isopropyl- 1,5,9-trimethyl-15- oxabicyclo [10.2.1] pentadeca-5,9-dien-2-ol	2.218	-2.303	-2.303	-0.105	-9.048
20	6436665/4,8,13- Cyclotetradecatriene- 1,3-diol, 1,5,9- trimethyl-12-(1- methylethyl)-	9.140	-2.283	-2.283	-0.104	-7.726
21	10979156/3E,7E,11E)- 1-Isopropyl-4,8,12- trimethylcyclotetradeca -3,7,11-trienol	5.391	-2.033	-2.033	-0.097	-8.938

22	567757/Verbenyl ethyl ether	26.708	-2.025	-2.025	-0.156	-5.837
23	15559762/Isopropyl-1,5,9-trimethyl-15-oxabicyclo [10.2.1]pentadeca-5,9-dien-2-ol	4.456	-1.842	-1.842	-0.084	-7.600
24	409383/Ethanone, 2-(4-morpholinyl)-1-phenyl	17.532	-1.841	-1.841	-0.123	-7.159
25	549059/Cyclopentanol, 1-(1-methylene-2-propenyl)-	20.511	-1.786	-1.786	-0.179	-6.985
26	86182191/5,5-Dimethyl-1-vinylbicyclo [2.1.1] hexane	39.760	-1.767	-1.767	-0.177	-4.710
27	90470329/1-Isopropyl-5,9,13-trimethyl-4,16-dioxatricyclo [11.2.1.03,5] hexadec-8-en-12-ol	16.469	-1.766	-1.766	-0.077	-7.765
28	524461/p-Mentha-1(7),8-dien-2-ol	3.124	-1.748	-1.748	-0.125	-7.572
29	5281384/(R,1E,5E,9E)-1,5,9-Trimethyl-12-(prop-1-en-2-yl) cyclotetradeca-1,5,9-triene	-5.069	-1.736	-1.736	-0.087	-6.258
30	580684/benzaldehyde, 4-(2-Chloro-benzyloxy)-3,5-dimethoxy-	30.723	-1.654	-1.654	-0.079	-8.461
31	21701008/Cyclopentane, 1-ethenyl-3-methylene-	2.874	-1.504	-1.504	-0.188	-5.100
32	557018/4-Cyclohexylidene-n-butanol	3.937	-1.466	-1.466	-0.133	-8.130
33	550119/2-Methyl-3-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-oxetane	-3.157	-1.161	-1.161	-0.073	-7.413
34	557032/1,2-Dipropylcyclopropene	-4.720	-0.828	-0.828	-0.092	-5.582
35	5367475/1,3-trans,5-cis-Octatriene	1.096	0.673	0.673	0.084	-5.18

36	5459291/Caparratriene	-5.007	2.161	2.161	0.144	-7.147
37	5280435/Phytol	9.563	2.313	2.313	0.110	-
						11.50
						0
38	141979/7-Tetradecyne	3.635	4.291	4.291	0.306	-7.623

Table 3 presents the molecular docking results of various phytochemicals identified through the GC-MS analysis of BSRE, with dopamine, a key neurotransmitter implicated in HFD related neurological diseases, as reported by Neuman et al. (2022) and Lauretani et al. (2024), alongside their docking scores arranged in decreasing affinity. Compounds numbered 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 22, 24, 25, 26, 27, 30, and 37 were noted to exhibit high binding energy values (kcal/mol) (both line energy > 5), suggesting weak modulating abilities as also postulated by (Owoloye et al., 2022). In contrast, nine compounds, numbered 3, 19, 23, 28, 29, 31, 32, 33, and 34, showed stronger binding affinities (binding energy < 5 kcal/mol) with favorable negative docking scores and Glide g-values, suggesting a high potential for dopamine receptor modulation. These include Cyclohexanone, 4-ethenyl-; (1S,2R,5E,9E,12R)-12-Isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol; Isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol; p-Mentha-1(7),8-dien-2-ol; (R,1E,5E,9E)-1,5,9-Trimethyl-12-(prop-1-en-2-yl)cyclotetradeca-1,5,9-triene; Cyclopentane, 1-ethenyl-3-methylene; 4-Cyclohexylidene-n-butanol; 2-Methyl-3-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-oxetane; and 1,2-Dipropylcyclopropene. Notably, some of these compounds further exhibited more favorable energy profiles than ascorbic acid, the reference agent. Conversely, compounds 35, 36, 37 and 38 demonstrated positive docking affinities and very high Glide ligand efficiencies, indicating limited pharmacological relevance. Overall, the variability in docking interactions suggests that the nine highlighted phytochemicals may represent the most promising candidates for modulating dopamine activity and possibly contributing to the extract's potential therapeutic and neuroprotective effects.

Table 4: MMGBSA Results of GC-MS Identified Phytoconstituents and Dopamine, along with Ascorbic acid as reference

No	COMPOUNDS' CID/IUPAC NAME	PUBCHEM	PRIME ENERGY (kcal/mol)	MMGBSA ΔG Bind (kcal/mol)	LIGAND ENERGY (kcal/mol)	MMGBSA ΔG Bind Coulomb	Complex Energy (kcal/mol)
1	5280435/Phytol		-30.100	-17.680	-10.011	-4.190	-30.149
2	580684/benzaldehyde, 4-(2-Chloro-benzyloxy)-3,5-dimethoxy-	4-(2-	11.400	-16.590	37.997	-2.450	11.383
3	5459291/Caparratriene		-41.500	-16.050	-22.959	-1.710	-41.472
4	576906/Trans-3-Caren-2-ol		-16.500	-15.910	1.851	-12.400	-16.519
5	6436665/4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)-		-84.300	-15.830	-65.982	-12.090	-84.273

6	5281384/(R,1E,5E,9E)-1,5,9-Trimethyl-12-(prop-1-en-2-yl)cyclotetradeca-1,5,9-triene	-51.300	-15.690	-33.153	-0.570	-51.301
7	141979/7-Tetradecyne	-18.200	-15.340	-0.436	-4.650	-18.241
8	90470329/1-Isopropyl-5,9,13-trimethyl-4,16-dioxatricyclo[11.2.1.03,5] hexadec-8-en-12-ol	-38.800	-14.740	-21.578	-2.100	-38.775
9	10979156/3E,7E,11E)-1-Isopropyl-4,8,12-trimethylcyclotetradeca-3,7,11-trienol	-51.400	-14.160	-34.740	-1.440	-51.356
10	15559762/Isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol	-41.100	-14.040	-17.016	-3.630	-41.077
11	10812/Benzene, 1-methyl-3-(1-methylethyl	-16.900	-13.940	-0.462	-0.410	-16.866
12	550119/2-Methyl-3-(3-methylbut-2-enyl)-2-(4-methylpent-3-enyl)-oxetane	-52.100	-13.150	-36.509	-0.460	-52.114
13	10703/O- Cymene	-10.800	-12.930	4.541	-0.240	-10.849
14	524461/p-Mentha-1(7),8-dien-2-ol	-52.900	-12.200	-38.221	-1.250	-52.878
15	21701008/Cyclopentane, 1-ethenyl-3-methylene-	-16.800	-11.560	-2.808	-0.350	-16.826
16	5365758/1,5-Cyclooctadiene, 1,5-dimethyl-	-20.400	-11.360	-6.581	-0.530	-20.404
17	244/Benzyl alcohol	-4.700	-11.270	9.043	-1.500	-4.687
18	557018/4-Cyclohexylidene-n-butanol	-19.700	-11.110	-6.083	-3.620	-19.656
19	5367475/1,3-trans,5-cis-Octatriene	-13.400	-10.880	-0.020	-1.200	-13.355
20	576718/1,3,5-Cycloheptatriene, 3,7,7-trimethyl-	-22.400	-10.800	-9.129	-0.070	-22.390
21	567757/Verbenyl ethyl ether	-10.200	-10.580	2.818	-1.930	-10.226
22	557032/1,2-Dipropylcyclopropene	-17.400	-10.570	-4.417	0.590	-17.447
23	6616/Camphene	-2.000	-10.540	18.601	-0.060	-1.956
24	564260/Bicyclo [3.1.0] hexan-3-ol, 4-methylene-1-(1-methylethyl)-, [1S-(1. alpha.,3. beta.,5. alpha.)]-	-14.800	-10.520	-1.784	-2.310	-14.762
25	86182191/5,5-Dimethyl-1-vinylbicyclo [2.1.1] hexane	8.100	-10.440	28.607	-0.820	8.150
26	21122289/Cyclohexane, 1,3-dimethyl-2-methylene-, cis	-14.000	-10.350	-1.143	0.190	-13.952
27	170833/Isopulegol	-18.900	-8.440	-7.968	-2.070	-18.873
28	89664/Trans-Verbena	-6.700	-7.790	3.521	-3.770	-6.729
29	6428442/Trans-p-mentha-1(7),8-dien-2-ol	-24.600	-7.580	-14.540	-3.630	-24.581

30	9904641/(1S,2R,5E,9E,12R)-12-Isopropyl-1,5,9-trimethyl-15-oxabicyclo [10.2.1] pentadeca-5,9-dien-2-ol	-36.800	-7.490	-19.283	-5.630	-36.791
31	549059/Cyclopentanol, 1-(1-methylene-2-propenyl)-	-6.100	-7.450	3.814	-4.130	-6.097
32	102667/Bicyclo[3.1.1] heptan-3-ol, 6,6-dimethyl-2-methylene-, [1S-(1. alpha.,3. alpha.,5. alpha.)]-	6.000	-7.340	15.824	-4.710	6.029
33	100031/1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo [4.1.0] heptan-2-one	-14.300	-7.270	-4.573	-4.190	-14.308
34	543953/Cyclohexanone, 4-ethenyl-	-25.700	-6.830	-16.437	-3.520	-25.724
35	537752/7-Oxabicyclo [4.1.0] heptane, 1,5-dimethyl-	-6.500	-6.760	2.724	-3.510	-6.496
36	543945/2,4-Dimethyl-3-nitrobicyclo [3.2.1] octan-8-one	33.200	-5.870	41.509	-1.830	33.176
37	409383/Ethanone, 2-(4-morpholinyl)-1-phenyl	60.700	-5.620	68.766	-4.920	60.688
38	92874/Bicyclo [3.1.1] hept-3-en-2-one, 4,6,6-trimethyl-, (1S)-	4.300	-5.450	12.181	-2.490	4.269
	Reference control					
39	54670067/Ascorbic Acid	-10.100	-4.390	4.353	-38.970	-10.055

Table 4 summarizes the MMGBSA binding free energy (ΔG bind) analysis of detected phytoconstituents from the GC-MS profile of *Boswellia dalzielii* stem bark and resin extract (BSRE), as docked with dopamine using ascorbic acid as a reference compound, and alongside their MMGBSA ΔG bind (kcal/mol) values arranged in order of reducing power. The first compound, Phytol, showed the most prominent MMGBSA ΔG bind of -17.680 kcal/mol, indicating a strong affinity for dopamine modulation as a potential drug candidate, surpassing that of reference ascorbic acid (-4.390 kcal/mol) and aligning with the prior reports of (Ylilauri & Pentikäinen, 2013) and (Hsieh et al., 2021). All the identified phytochemicals also demonstrated stronger MMGBSA binding energies than the control, with only 27 metabolites (Compounds 1, 3–16, 18–22, 24, 26–27, 29–30, 33–34) showing superior prime energies, including the previously identified top nine candidates. While ascorbic acid showed a moderate prime energy (-10.100 kcal/mol) and ligand energy (4.353 kcal/mol), approximately 71.05% of the BSRE-derived compounds outperformed the reference agent across all MMGBSA scoring metrics in table 4 above, suggesting more spontaneous and stable bioactivity. Conversely, Compounds 2, 17, 23, 25, 28, 31, 32, and 35–38 exhibited relatively unfavorable prime and ligand energies, despite possessing MMGBSA ΔG bind values that were better than the reference. Consequently, the nine top-performing compounds, Cyclohexanone, 4-ethenyl-; (1S,2R,5E,9E,12R)-12-Isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol; Isopropyl-1,5,9-trimethyl-15-oxabicyclo [10.2.1] pentadeca-5,9-dien-2-ol; p-Mentha-1(7),8-dien-2-ol; (R,1E,5E,9E)-1,5,9-Trimethyl-12-(prop-1-en-2-yl)cyclotetradeca-1,5,9-triene; Cyclopentane, 1-ethenyl-3-methylene; 4-Cyclohexylidene-n-butanol; 2-Methyl-3-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-oxetane; and 1,2-Dipropylcyclopropene showed consistently moderated MMGBSA profiles,

outperforming ascorbic acid across multiple biochemical contexts and hence strongly recommended as promising candidates or adjunct agents in modulating dopaminergic activity.

Table 5: ADMET Results of GC-MS Identified Phytoconstituents and the Standard Agent, Ascorbic Acid

No	Compounds' Pubchem CID/Iupac Name	Rule of five violated	Molecular weight	AcceptHB	DonorHB	QPlog Po/w	Human Oral Absorption	Percent Human Oral Absorption
1	244/Benzyl alcohol	0.000	108.140	1.700	1.000	1.101	3.000	95.740
2	5367475/1,3-trans,5-cis-Octatriene	0.000	108.183	0.000	0.000	4.089	3.000	100.000
3	21701008/Cyclopentane, 1-ethenyl-3-methylene-	0.000	108.183	0.000	0.000	3.294	3.000	100.000
4	543953/Cyclohexanone, 4-ethenyl-	0.000	124.182	2.000	0.000	1.536	3.000	100.000
5	557032/1,2-Dipropylcyclopropene	0.000	124.225	0.000	0.000	4.121	3.000	100.000
6	21122289/Cyclohexane, 1,3-dimethyl-2-methylene-, cis	0.000	124.225	0.000	0.000	3.396	3.000	100.000
7	537752/7-Oxabicyclo[4.1.0]heptane, 1,5-dimethyl-	0.000	126.198	2.000	0.000	1.250	3.000	100.000
8	576718/1,3,5-Cycloheptatriene, 3,7,7-trimethyl-	0.000	134.221	0.000	0.000	3.669	3.000	100.000
9	10703/O-Cymene	0.000	134.221	0.000	0.000	3.628	3.000	100.000
10	10812/Benzene, 1-methyl-3-(1-methylethyl	0.000	134.221	0.000	0.000	3.808	3.000	100.000
11	5365758/1,5-Cyclooctadiene, 1,5-dimethyl-	0.000	136.236	0.000	0.000	3.770	3.000	100.000
12	86182191/5,5-Dimethyl-1-	0.000	136.236	0.000	0.000	3.541	3.000	100.000

	vinylbicyclo[2.1.1]]hexane							
13	6616/Camphene	0.00 0	136.236	0.000	0.000	3.310	3.000	100.000
14	549059/Cyclopent anol, 1-(1- methylene-2- propenyl)-	0.00 0	138.209	0.750	1.000	2.457	3.000	100.000
15	92874/Bicyclo[3.1 .1]hept-3-en-2- one, 4,6,6- trimethyl-, (1S)-	0.00 0	150.220	2.000	0.000	1.890	3.000	100.000
16	564260\Bicyclo[3. 1.0]hexan-3-ol, 4- methylene-1-(1- methylethyl)-, [1S- (1.alpha.,3.beta.,5. alpha.)]-	0.00 0	152.236	1.700	1.000	2.197	3.000	100.000
17	102667\Bicyclo[3. 1.1]heptan-3-ol, 6,6-dimethyl-2- methylene-, [1S- (1.alpha.,3.alpha., 5.alpha.)]-	0.00 0	152.236	1.700	1.000	2.064	3.000	100.000
18	89664/Trans- Verbeno	0.00 0	152.236	1.700	1.000	2.075	3.000	100.000
19	6428442/Trans-p- mentha-1(7),8- dien-2-ol	0.00 0	152.236	1.700	1.000	2.436	3.000	100.000
20	576906/Trans-3- Caren-2-ol	0.00 0	152.236	1.700	1.000	2.095	3.000	100.000
21	170833/Isopulegol	0.00 0	154.252	1.700	1.000	2.715	3.000	100.000
22	557018/4- Cyclohexylidene- n-butanol	0.00 0	154.252	1.700	1.000	2.311	3.000	100.000
23	100031/1-methyl- 4-(prop-1-en-2- yl)-7- oxabicyclo[4.1.0]h eptan-2-one	0.00 0	166.219	4.000	0.000	1.012	3.000	96.697
24	Reference control 54670067/Ascorb ic Acid	0.00 0	176.126	7.900	4.000	-1.852	2.000	44.781

25	567757/Verbenyl ethyl ether	0.00 0	180.289	1.700	0.000	2.594	3.000	100.000
26	524461/p-Mentha-1(7),8-dien-2-ol	0.00 0	194.273	2.000	0.000	3.107	3.000	100.000
27	141979/7-Tetradecyne	1.00 0	194.359	0.000	0.000	6.725	1.000	100.000
28	543945/2,4-Dimethyl-3-nitrobicyclo[3.2.1]octan-8-one	0.00 0	197.233	4.000	0.000	0.866	3.000	83.717
29	409383/Ethanone, 2-(4-morpholinyl)-1-phenyl	0.00 0	205.256	5.700	0.000	0.672	3.000	85.251
30	5459291/Caparratriene	1.00 0	206.370	0.000	0.000	6.803	1.000	100.000
31	550119/2-Methyl-3-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-oxetane	0.00 0	222.370	2.000	0.000	3.363	3.000	100.000
32	5281384/(R,1E,5E,9E)-1,5,9-Trimethyl-12-(prop-1-en-2-yl)cyclotetradeca-1,5,9-triene	1.00 0	272.473	0.000	0.000	6.507	1.000	100.000
33	10979156/3E,7E,11E)-1-Isopropyl-4,8,12-trimethylcyclotetradeca-3,7,11-trienol	1.00 0	290.488	0.750	1.000	5.495	1.000	100.000
34	5280435/Phytol	1.00 0	296.535	1.700	1.000	5.819	3.000	100.000
35	15559762/Isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol	0.00 0	306.487	2.450	1.000	4.875	3.000	100.000
36	9904641/(1S,2R,5E,9E,12R)-12-Isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]	0.00 0	306.487	2.450	1.000	4.781	3.000	100.000

	pentadeca-5,9-dien-2-ol							
37	6436665/4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)-	0.00	306.487	2.450	2.000	4.479	3.000	100.000
		0						
38	580684/benzaldehyde, 4-(2-Chlorobenzyloxy)-3,5-dimethoxy-	0.00	306.745	4.250	0.000	3.313	3.000	100.000
		0						
39	90470329/1-Isopropyl-5,9,13-trimethyl-4,16-dioxatricyclo[11.2.1.0 ^{3,5}]hexadec-8-en-12-ol	0.00	322.487	4.450	1.000	4.021	3.000	100.000
		0						

Table 5 presented the ADMET results for various phytoconstituents identified from the GC-MS analysis of BSRE and their comparison with ascorbic acid as a reference benchmark, alongside their molecular weights arranged in ascending order. The first compound, benzyl alcohol, illustrated the lowest molecular weight of 108.14 g/mol, suggesting it may easily permeate biological membranes, as supported by its Percent Human Oral Absorption of 95.740%. The subsequent compounds from number 2 - 23, such as 1,3-trans,5-cis-Octatriene and Cyclopentane derivatives, exhibited relatively low molecular weight variations and high oral absorption, exceeding the reference compound, further indicating good bioavailability. The table further demonstrated that the first twenty-six phytoconstituents fully complied with Lipinski's Rule of Five, showing zero violations and Percent Human Oral Absorption values ranging from 95.740% to 100%, characteristics that typically associated with favorable oral pharmacokinetics as reported by (Roskoski, 2023). Among the nine previously identified lead compounds, eight {Cyclohexanone, 4-ethenyl-; (1S,2R,5E,9E,12R)-12-Isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol; Isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol; p-Mentha-1(7),8-dien-2-ol; Cyclopentane, 1-ethenyl-3-methylene; 4-Cyclohexylidene-n-butanol; 2-Methyl-3-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-oxetane; and 1,2-Dipropylcyclopropene} met all of Lipinski's criteria, while only (R,1E,5E,9E)-1,5,9-Trimethyl-12-(prop-1-en-2-yl)cyclotetradeca-1,5,9-triene exhibited a single violation. These findings further validated the pharmacokinetic suitability of the eight out of nine top-rated candidates as potential dopamine modulators, suggesting BSRE, offering superior efficacy, bioavailability, and safety profiles compared to reference ascorbic acid, thereby supporting its promise in the development of novel neuropharmacological agent.

Histopathology of male and female rats' brains assaulted with HFD and co-treated

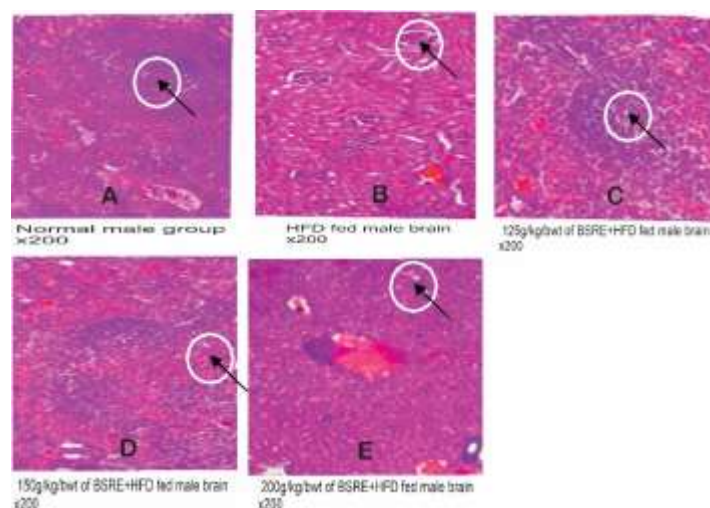


Figure 10: Male brain histology

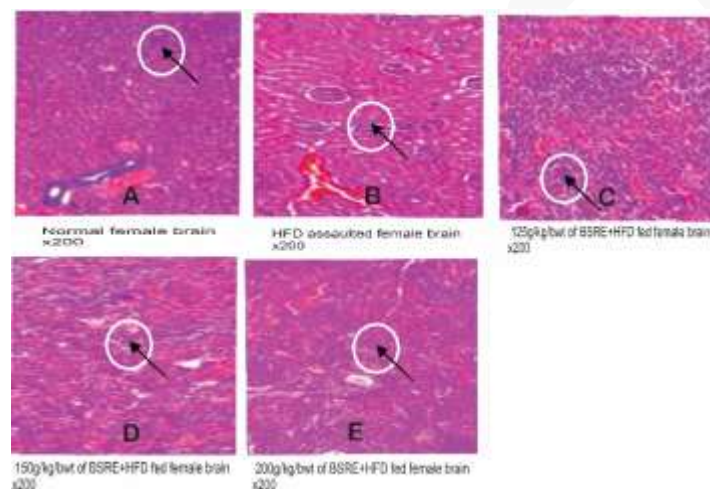


Figure 11: Female brain histology

Figures 10 and 11: Sectional photomicrograph (mag x200 H&E&G) of male and female rats' brains subjected to a high-fat diet. A- Normal group. B- High-fat diet (HFD) fed group. C- HFD+125mg/kg/bwt of BSRE. D- HFD+150mg/kg/bwt of BSRE. E- HFD+200mg/kg/bwt of BSRE. White arrows indicate intrinsic brain steatosis, hippocampal, hypothalamic, and neurological inflammation.

The brain tissue of the normal male and female groups, as shown in Figures 10A and 11A, appears healthy, exhibiting a typical structure with no signs of inflammation or damage in the hippocampus (Lin et al., 2021) and the hypothalamus (Sanetra et al., 2023). In contrast, the brains of male and female rats subjected to a high-fat diet (HFD) show significant alterations, including fat accumulation and lipidosis (Olešová et al., 2024) in the cortex (Masetto Antunes et al., 2022), amygdala, and striatum, accompanied by steatosis, compromising neuronal synapses and cognitive functions (Neuman et al., 2022). However, co-treatment with BSRE demonstrated neuroprotective effects, potentially reducing inflammation and restoring cellular architecture to near-normal levels.

Specifically, group 11C and 11D for females, which received HFD+125 and HFD+150 mg/kg BSRE of the extract, exhibited enhanced protective effects than Group 11E (200mg/kg of BSRE), potentially resulting in better preservation of the hippocampus and hypothalamus, the key regions for learning and memory, suggesting hormetic recovery. Additionally, group 10E for males, co-treated with HFD and 200 mg/kg BSRE, further exhibited pronounced benefits compared to 10C and 10D that were co-administered 125 and 150mg/kg/bwt, indicating a dose-dependent response of BSRE in mitigating the adverse effects of HFD. This denotes hormonal resiliency to the agonist in the female rats co-treated with the extracts (Zhang et al., 2002).

Discussion

It was established in this study that the combined aqueous ethanolic di-herbal extract of *Boswellia dalzielii* resin and stem bark (BSRE) disclosed stronger free-radical scavenging activity than the individual resin (BRE) or stem bark extract (BSE with accomplished in-vivo neuroprotective, anti-dyslipidemic, and antioxidant potential in high-fat diet (HFD)-induced metabolic dysfunctions in male and female Wistar rats. These were noted to be driven by the synergetic activities of GCMS identified metabolites with favourable pharmacokinetic, docking, ligand efficiency along with zero Lipinski rules of five violation. Additionally, through comprehensive GC-MS profiling, in-silico molecular modeling, and pre-clinical evaluation, the results further established the hormonal resilient responses of the female rat gender and eight categorized phytochemicals which are key in BSRE potency. The GC-MS analysis specifically identified thirty-eight (38) phytochemicals in BSRE, with three of them; Isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol, (1S,2R,5E,9E,12R)-12-Isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol, and benzaldehyde, 4-(2-chlorobenzyloxy)-3,5-dimethoxy-, dominating 64.27% of the total. These major compounds, together with smaller concentrated ones, vis-a-vis 7-oxabicyclo[4.1.0]heptane, 1,5-dimethyl-, 4-cyclohexylidene-n-butanol, and phytol, are likely responsible for the stronger effects seen with the combined extract during chelating comparism. The findings further supported the reports of (Salisu et al., 2018), (Yakubu et al., 2020), and (Medugu et al., 2020b) on the pharmacological value of *B. dalzielii*. Molecular docking against the dopamine receptor identified nine compounds with strong binding energies (MMGBSA $\Delta G < -5$ kcal/mol). These are Cyclohexanone, 4-ethenyl-; (1S,2R,5E,9E,12R)-12-Isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol; Isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol; p-Mentha-1(7),8-dien-2-ol; (R,1E,5E,9E)-1,5,9-Trimethyl-12-(prop-1-en-2-yl) cyclotetradeca-1,5,9- triene; Cyclopentane, 1-ethenyl-3-methylene; 4-Cyclohexylidene-n-butanol; 2-Methyl-3-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-oxetane; and 1,2-Dipropylcyclopropene with also better docking scores and glide g values than the reference antioxidant ascorbic acid. Ligand efficiency analysis further confirmed the spontaneous modulating abilities of these key nine (9) phytochemicals, well above that of the reference control, while also conforming with the accounts of (Ylilauri & Pentikäinen, 2013) and (Hsieh et al., 2021). Over 71.05% of BSRE compounds demonstrated stronger and favorable MMGBSA scoring profiles than ascorbic acid, affirming their therapeutic relevance in modulating dopaminergic pathways. In contrast, the compounds Benzaldehyde, 4-(2-Chloro-benzyloxy)-3,5-dimethoxy-; Benzyl alcohol; Camphene; 5,5-Dimethyl-1-vinylbicyclo[2.1.1]hexane; Trans-Verbeno; Cyclopentanol, 1-(1-methylene-2-propenyl)-; Bicyclo[3.1.1]heptan-3-ol, 6,6-dimethyl-2-methylene-, [1S-; 7-Oxabicyclo[4.1.0]heptane, 1,5-dimethyl-; 2,4-Dimethyl-3-nitrobicyclo[3.2.1]octan-8-one; Ethanone, 2-(4-morpholinyl)-1-phenyl; and Bicyclo[3.1.1]hept-3-en-2-one, 4,6,6-trimethyl-, (1S)- displayed relatively unfavorable prime and ligand energies, even

though their MMGDSA ΔG bind values were better than the control, debuting their well proclaimed anti-oxidant efficacies to a certain extent. ADMET screening further showed that most of the top-ranked compounds met Lipinski's Rule of Five and have high predicted oral absorption (95.740 – 100%), while only one compound, (R,1E,5E,9E)-1,5,9-trimethyl-12-(prop-1-en-2-yl) cyclotetradeca-1,5,9-triene, violated a single rule, indicating that eight candidates could be presented with the best favorable drug-like properties. These findings can hence support their development as orally active pharmacological candidates (Roskoski, 2023).

More so, BSRE displayed potent antioxidant capacity across tested chelating assays of Fe^{2+} , where the combined extract outperformed the individual extracts (BRE and BSE), approaching those of standard ascorbic antioxidants. This suggests the synergistic interactions and possible therapeutic potencies of di-herbal combination of resin and stem bark phytocompounds and likely attributed to the hydrogen-donating capacity of BSRE phytocompounds, at adjunct consideration better than standard ascorbic acid. In the animal study, HFD study further showed a significant increase in brain weight, lipid peroxidation (MDA), myeloperoxidase (MPO) activity, and serum Castelli's Risk Index I (Yıldız et al., 2016) while reducing dopamine, catalase, Gpx, and reduced GSH levels especially in both gender. These accounts signify neurodegeneration, oxidative stress, and cardiometabolic related diseases, while co-treatment with BSRE, however, ameliorated these metabolic disturbances, often in a dose-dependent manner in male groups. Notably, male rats responded to higher doses (200 mg/kg) with significant recovery in brain weight and oxidative markers, while females exhibited quicker recovery at lower doses (125–150 mg/kg), suggesting hormone-mediated resilience (Hewagalamulage et al., 2016) and with hormetic effect at the highest dose, especially in the female brain (Skaperda et al., 2022).

Similarly, Dopamine and MPO level, which HFD disoriented, also recuperated by the co-treatment of BSRE in both sexes, though males displayed more robust recovery at higher doses while females recuperated at lower intramuscularly administered doses. Antioxidant enzymes, including catalase, Gpx, and GSH, followed a similar trend, indicating the extract's efficacy in reversing HFD-induced oxidative cascade, most importantly due to the higher activities of antioxidant status recorded in females than males when compared.

Histologically, BSRE protected neuronal architecture from HFD-induced damage, particularly in the hippocampus (Lin et al., 2021) and hypothalamus (Sanetra et al., 2023). Female rats showed hormetic recovery (Scuto et al., 2024) at lower doses (Nazari & Moosavi, 2022), while male rats required higher doses to achieve similar outcomes. This aligns with the known neuroprotective influence of higher levels of estrogen and oxytocin, which have been established to enhance redox adaptability and control blood-brain barrier permeability, most especially in females (Bake et al., 2014). Moreover, BSRE significantly lowered Castelli's Risk Index I in both sexes, indicating cardioprotective potential and thus a better robust activity of high-density lipoprotein cholesterol in reverse trafficking of low-density lipoprotein cholesterol back to the liver. Finally, males demonstrated a more vulnerable status to HFD-induced dysfunctions and required higher doses of the extract for full recovery, whereas females mostly reached near-normal levels across lesser doses when compared.

Conclusion

This study established the neuroprotective, anti-adiposity, anti-dyslipidemic, and antioxidant effects of combined aqueous ethanolic di-herbal extract of *Boswellia dalzielii* stem bark and resin (BSRE), especially against high-fat diet (HFD)-related metabolic derangements. Laboratory tests, GC-MS analysis, computer docking, free-energy calculations, ADMET predictions, and tissue

examinations further supported this affirmation. While BSRE contains many active plant GCMS detected compounds that bind well to dopamine receptors, signalling good drug-like properties, lowering blood lipids, and strongly scavenging free radicals. The results also unfolded eight main compounds that supported Lipinski's rules of five among others and hence look promising for further pharmacognostic development. These include the two most abundant plant reductants namely (1S,2R,5E,9E,12R)-12-isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol and isopropyl-1,5,9-trimethyl-15-oxabicyclo[10.2.1]pentadeca-5,9-dien-2-ol, along with cyclohexanone, 4-ethenyl-, p-mentha-1(7),8-dien-2-ol; cyclopentane, 1-ethenyl-3-methylene; 4-cyclohexylidene-n-butanol; 2-methyl-3-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-oxetane; and 1,2-dipropylcyclopropene. Hence, all eight phytochemicals are recommended candidates for dopamine-related neuroprotective drugs and HFD related impairments. Histological results further confirmed these predictions, showing that BSRE reduced excess brain steatosis and ameliorated HFD-induced brain cell damage, while also normalizing the reduction in dopamine levels, lipid peroxidation (MDA), and the elevated Castelli's Risk Index-I., with female rats responded better at lower doses than male rats. This is linked to the higher levels of catalase and glutathione as established and possibly to the protective effects of the hormonal moderating abilities on the oxidative defense pathways in the female animals.

In conclusion, BSRE is a promising plant-based option for reducing neurological, cardiovascular, and oxidative problems caused by a high-fat diet. Hence, further studies are needed to confirm its safety and effectiveness in clinical study and to evaluate the stability, half-life, and pharmacognostic applicability of the eight lead GCMS detected phyto-compounds.

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Conflicts of Interest

The authors further state that there are no conflicts of interest regarding the manuscript.

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Authors Contribution

All authors were pre-informed about this manuscript. Most importantly, TIF, ACA, TMO and AAA, provided the concept and design; TMO and ACA supervised the desk analysis; TIF, OGO, and SBA engaged in data acquisition, molecular docking, data analysis, experimental studies, while TIF and ACA authenticated the galenic and helped in sourcing and drying; TIF, OGO, and SBA did the extraction, assayed and quantified all biomarkers of interest, cared for and sacrificed the experimental rats; TIF evaluated the phytochemical analysis of the plant, proceeded with the literature search and manuscript preparation/submission, while ACA and AAA reviewed the manuscript.

Ethical Protocol

The ethical guideline was endorsed by the Institutional Animal Care Committee of the Institution and conforms with the guidelines stated by the Center for Research and Development (CERAD), Federal University of Technology, Akure (FUTA) and Nigeria College of Natural Medicine Technology (NICONMTECH) (accredited), Federal Ministry of Innovation, Science, and Technology; co-monitored by the Department of Biochemistry, Federal University of Technology, Akure (FUTA), and guided by the laydown rules and regulations of the National Institute of Health (NIH), (1985) and Institute of Laboratory Animal Resources, National Institutes of Health, USA, 1996.

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