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Honey: A remedy for depression. An investigation by experimental validation and molecular docking studies

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Abstract
Depression also known as clinical depression, is a mental disorder of public health concern that should be properly and immediately treated because a poor medical follow up can lead to suicide resulting to death or major body self-infliction of harm. Prediction of the phytochemical compounds in honey on neurotransmitters and enzymes involved in depression were investigated by *in-silico* studies. This research was done to create docking scores, predict pharmacodynamics of honey and to identify the potential oral drugs used for the treatment of depression Studies have shown that honey and related by products like propolisto be very useful in the treatment of depression. In this preclinical research, animal models was used to demonstrate the antidepressant effect of honey on female albino mice. These tests included tail suspension test and forced swim test, during which they were shared into four groups. From the results obtained honey showed a promising antidepressant activity together with a better synergism with imipramine.
From the molecular docking scores obtained, honey was found to have phytochemical compounds (examples) with good potentials to be oral antidepressants especially Chlorogenic acid.

Keywords: depression, honey, imipramine, molecular docking, virtual screening

Introduction

Depression is a mental condition characterized by feelings of severe despondency and dejection, typically also with feelings of inadequacy and guilt, often accompanied by lack of energy and disturbance of appetite and sleep (Farrell, 2020). The burden of depression and other mental health conditions is on the rise globally. According to WHO, over 264 million people suffer from depression (WHO, 2020) [31].

Depression is a mental disorder that so many persons suffer from and may not know they do, hence do not get proper medication and treatment follow up. Gradually the individual starts manifesting clinical symptoms like withdrawal, pharmaco-dependence, drug abuse and addiction and eventually showing suicidal behaviors.

Although there are known antidepressants such as SSRIs, TCAS and SNRIs, but their inability to produce complete recovery in addition to their debilitating side effects, lack of access to these medication and high cost, have forced the need by researchers to find more acceptable and effective natural alternatives. In the recent times, some research studies have implicated honey as a potential antidepressant (Ali and Hendawy, 2018) [1].

Honey is an organic natural substance, produced from the nectar of flowers by *Apis mellifera* and it is a sweet, flavoured liquid. It contains sugars, small quantities of proteins, enzymes, amino acids, minerals, trace elements, vitamins, aroma compounds, and polyphones (Ali and Hendawy, 2018) [1]. Honey is widely accepted as food and medicine by all generations, traditions and civilizations, both ancient and modern.

Honey has also been used recently for the treatment of several gastrointestinal, cardiovascular, inflammatory and neoplastic states (Eteraf-Oskouei and Najafi. 2013) [9]. Somehow, literature indicates that bee honey can be beneficial for people with psychiatric and mental health problems (Munstedt *et al*., 2015) [19]. Depression is considered as an imbalance of neurotransmitters and the production of the neurotransmitters is catalysed by various enzymes directly or indirectly.

Inhibition of Monoamine oxidase (MAO): this is an enzyme responsible for the breakdown of monoamines. There are two types of monoamine oxidase which are MAO-A and B. They are found in the CNS, (particularly in the neurons and astroglia). MAO-A and MAO-B are FAD-dependent enzymes responsible for the metabolism of neurotransmitters such as dopamine, serotonin, adrenaline, and noradrenaline and for the inactivation of exogenous aryl alkyl amines. They bind to the mitochondrial outer membrane and catalyse the oxidative deamination of their substrates. MAO-A mainly metabolizes 5-HT, dopamine (DA) and norepinephrine (NE) (Chaurasiya *et al.*, 2014) [5].

Inhibition of Cyclooxygenase; Cyclooxygenase (COX) exists in two isoforms, COX-1 and COX-2. COX-1 is constitutively expressed in the gastrointestinal tract whereas the COX-2 predominates at sites of inflammation. COX-1 is a constitutive

enzyme, whereas COX-2 is inducible, short-lived and is responsible for the biosynthesis of prostaglandins in inflammatory cells and CNS. COX-2 is known to interact with neurotransmitters such as acetylcholine, serotonin, and glutamate. COX-2 contributes to the pathogenesis of the depressive disorder (Müller *et al*., 2009) [18].

Nitric oxide synthase catalyses the production of nitric oxide (NO) which plays an important role in the pathogenesis of mood disorders, and has been implicated in the pathophysiology of depression. Higher concentration of plasma NO in patients with the recurrent depressive disorder was associated with the severity of depressive symptom suggesting that an overproduction of NO results in oxidative stress and cell damage. Increased production of NO and peroxynitrite may cause nitration and nitrosylation of proteins that appear to be related to the pathogenesis of depression. NO modulate 5-HT release from specific brain structures, affect 5-HT re-uptake and appears to interact with selective 5-HT reuptake inhibitors used in the treatment of depression. Several studies have demonstrated that NOS inhibitors produce antidepressant-like actions in a variety of animal paradigms (Morris and Berk, 2015) [7].

Matrix metalloproteinases (MMPs) are a family of neutral proteases that contributes to interactions between cells and their matrix, allowing movement and shape changes in processes such as development and neuronal plasticity. Oxygen radicals, NO and proteases have been implicated in MMP activation. MMP-9 serum levels significantly correlated with the depressive phases in younger subjects (<45yo) (Drago *et al*., 2014) [7]. This study aimed at evaluating the antidepressant activity of honey as well as the prediction of drug candidates with respect to the likely mechanisms of antidepressant actions.

Materials and Methods

Collection and identification of honey

Fresh honey (*a. mellifera*) was purchased from madonna university monastery. it was identified in the department of pharmacognosy, faculty of pharmacy, madonna university elele.

Preparation and administration of honey

Honey was weighed by measuring 10mls of honey using a measuring cylinder which was poured into beaker and it was weighed to get 15gram, therefore 10ml of honey weighs 15grams of honey. Then 10ml of honey was dissolved in 100ml of water. The colour of the dissolved honey was lighter in colour which gave a yellowish brown colour. 2.4g/kg of honey was administered to the female Albino mice 30mins before each of the experiment.

Collection, preparation and administration of the standard drug

Accord^{R} imipramine 10mg tablet was purchased from pharmacy at Owerri, Nigeria. A 10mg tablet was dissolved in 50ml of water. 30mg/kg of imipramine was administered to the mice 30mins before each of the experiments.

Experiment animal

Twelve female Albino mice weighing 18-26g were obtained from the Animal farm of the department of Pharmacology and Toxicology, Madonna University. They were housed in four cages A, B, C and D. They were fed the standard animal feed and fresh water was also provided for them. The animals were kept in line with laid down principles for animal care as prescribed in Helsinki's 1964 declaration. Ethical approval was given by the animal ethics committee of Madonna University, Ehthics committee-MAD/PHA/3009.

The mice were grouped randomly. n=3.

Tail suspension test

This was carried out as decribed by Steru *et al*. (1985) [29]

Forced swim test

As described by (Porsolt *et al*., 1977a, Porsolt *et al.,* 1977b) [22, 23].

Statistical analysis

Data were analyzed, using graph pad prism (9.1.0.221). Data with two or more independent variables, were analyzed using two-way analysis of variance (ANOVA) followed by Bonferonni's posttest, to compare replicate means by role. p values < 0.05, 0.001 and 0.0001 were considered significant.

In-silico studies

Ligand library generation

Identified secondary metabolites of *A. mellifera* employed for this study were determined from published literature and were used in the creation of the ligand library. Sixty one (61) secondary metabolites; Acacetin, Isorhamnetin, myricetin Hesperetin, luteolin Ferreres *et al.,* (1994) [11]. Kaempferol (Ferreres *et al.,* 1998) [12]. Ellagic acid, caffeic acid, coumaric acid, ferulic acid (Tomás-Barberán *et al.,* (2001) [30]. Phenylalanine, proline, tyrosine, glutaminic acid, serine, methionine, cysteine, leucine, isoleucine, lysine, valine, threonine, arginine, histidine, glycine, tryptophan, alanine, 4-hydroxyproline, aspartic acid (Hermosín *et al.,* 2003) [13]. Apigenin, genistein, pinocembrin, chrysin, quercetin, kaempferol, galangin, pinobanksin, 4-(dimethylamino)benzoic acid, gallic acid, vallinic acid, syringic acid, chlorogenic acid (Cianciosi *et al.,* (2018) [6]. Sucrose, maltose, isomaltose, panose, erlose, melezitose, trehalose (Ouchemoukh *et al.,* (2010) [20]. Kojibiose, nigerose, gentiobiose, laminaribiose, turanose (Siddiqui and Furgala, 1967) [28]. Were retrieved from NCBI PubChem library, in Standard Database Format (2D) (Ehigiator *et al*., 2020) [8]. The ligand library generated was imported to a docking software (Maestro) and prepared using the (Schrodinger suite version 2018-1b), as described by (Brooks *et al.,* 2008) [8].

Protein preparation

Structures of; Human hydrolase matrix metalloproteinase-2, Human hydrolase matrix metalloproteinase-3, Human hydrolase matrix metalloproteinase-9 Human monoamine oxidase B, Human Monoamine Oxidase A, Cyclooxygenase active site of cox-2, Human endothelial nitric oxide synthase and Human Histone deacetylase-2 (HDAC). Bound with ligands were retrieved from the Protein Data Base according to (Berman *et al*., 2000). With the PDB ID: 1HOV, 4G9L, 6ESM, 1OJA, 2Z5X, 1PXX, 6PP1, 4LXZ. They were prepared, using the Protein Preparation Wizard as described by (Sastry *et al*., 2013) [25]. Module in maestro 11.5 was used to prepare each protein complex. Missing hydrogen atoms, missing loop, and missing side-chains of protein structure were fixed while the added

hydrogen atoms were optimized at pH 7.0. Optimized structures were then minimized using the OPLS3 force field by converging heavy atoms to root mean square deviation (RMSD) of 0.3Å (Sastry *et al*., 2013) [25].

Pharmacokinetic parameters (ADME/TOX Prediction)

The pharmacokinetic properties of the hit compounds were estimated using the Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) of the hit ligands were predicted using the Qikprop module in maestro 11.5. (Schrödinger Release 2018-1c) [27].

Results

Effect of *A. mellifera* (Honey) on immobility time in tail suspension test after 360 seconds

As shown in figure 1, the immobility time in mice to which 5g/Kg honey alongside 30 mg/Kg imipramine were administered (Group D), showed significantly ($p<0.05$) shorter immobility time compared to control. Although, the group administered only honey 5 g/Kg (group B) and imipramine 30 mg/Kg (Group C) presented with shorter immobility time, compared to the untreated group (control) had no significant difference compared to control ($p>0.05$).

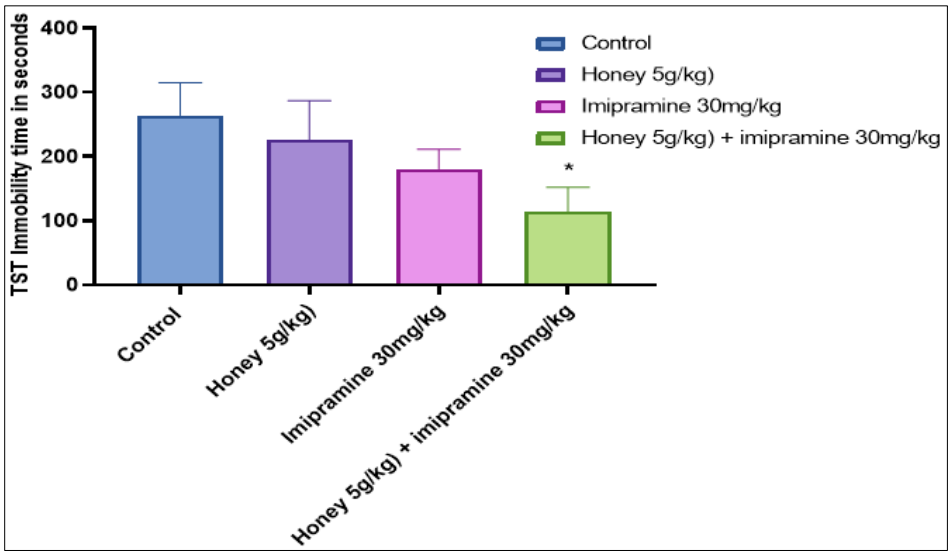

Fig 1: Effect of *A. mellifera* (Honey) on immobility time in Tail suspension test after 360 seconds. Animals per group (n) = 3. The values are mean ± SEM.; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ when compared with control group. (Two-way ANOVA followed by Bonferonni post hoc test).

Effect of *A. mellifera* (Honey) on immobility time in forced swim test after 360 seconds

As shown in figure 1, the immobility time in mice to which 5g/Kg honey alongside 30 mg/Kg imipramine were administered (Group D), showed significantly ($p<0.05$) shorter immobility time compared to control. Although, the group administered only honey 5 g/Kg (group B) and imipramine 30 mg/Kg (Group C) presented with shorter immobility time, compared to the untreated group (control) had no significant difference compared to control ($p>0.05$).

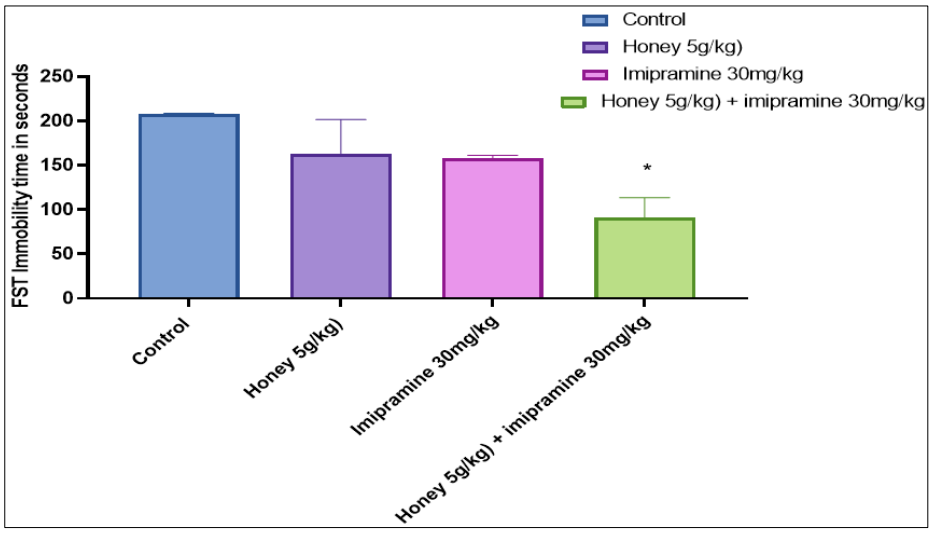

Fig 2: Effect of *A. mellifera* (Honey) on immobility time in forced swim test after 360 seconds. Animals per group (n) = 3. The values are mean ± SEM.; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ when compared with control group. (Two-way ANOVA followed by Bonferonni post hoc test).

Heat map representation of docking result for compound interaction with the catalytic domain of Human hydrolase matrix metalloproteinase-2 (MMP-2) complex

Docking results here showed that compounds such as; Chlorogenic acid, coumaric acid and myricetin have high affinity for the the catalytic domain of Human hydrolase matrix metalloproteinase-2 (MMP-2) complex. Upon antagonism, they may well be good potential drugs that may cat via this mechanism

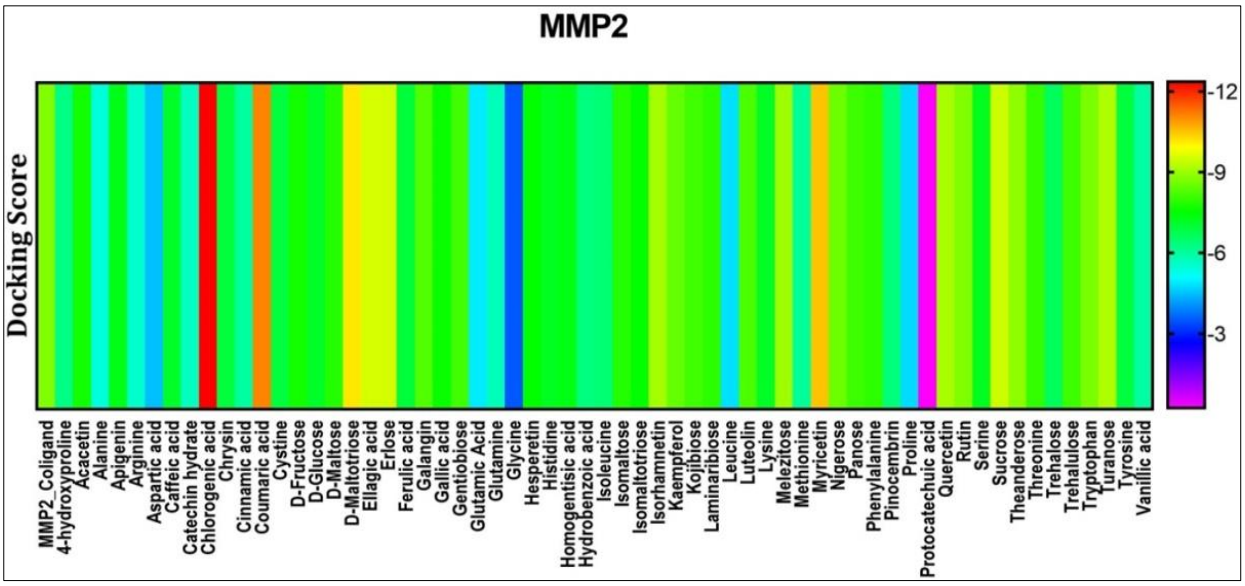

Fig 3: Heat map representation of docking result for compound interaction with the catalytic domain of Human hydrolase matrix metalloproteinase-2 (MMP-2) complex The free energy binding of phytochemicals of *A. mellifera* docked into the substrate binding site of Hydrolase matrix metalloproteinase-2 (MMP-2) complex, compared with the antagonist, sc-74020 and represented as heat map. (The scale is a spectrum from purple (-2 kcal/mol) to red (-12 kcal/mol).

Heat map representation of docking result for compound interaction with the catalytic domain of Human hydrolase matrix metalloproteinase-3 (MMP-3) complex

Docking results here showed that compounds such as; Chlorogenic acid, coumaric acid have high affinity for the the catalytic domain of Human hydrolase matrix metalloproteinase-3 (MMP-3) complex. Upon antagonism, they may well be good potential drugs that may cat via this mechanism

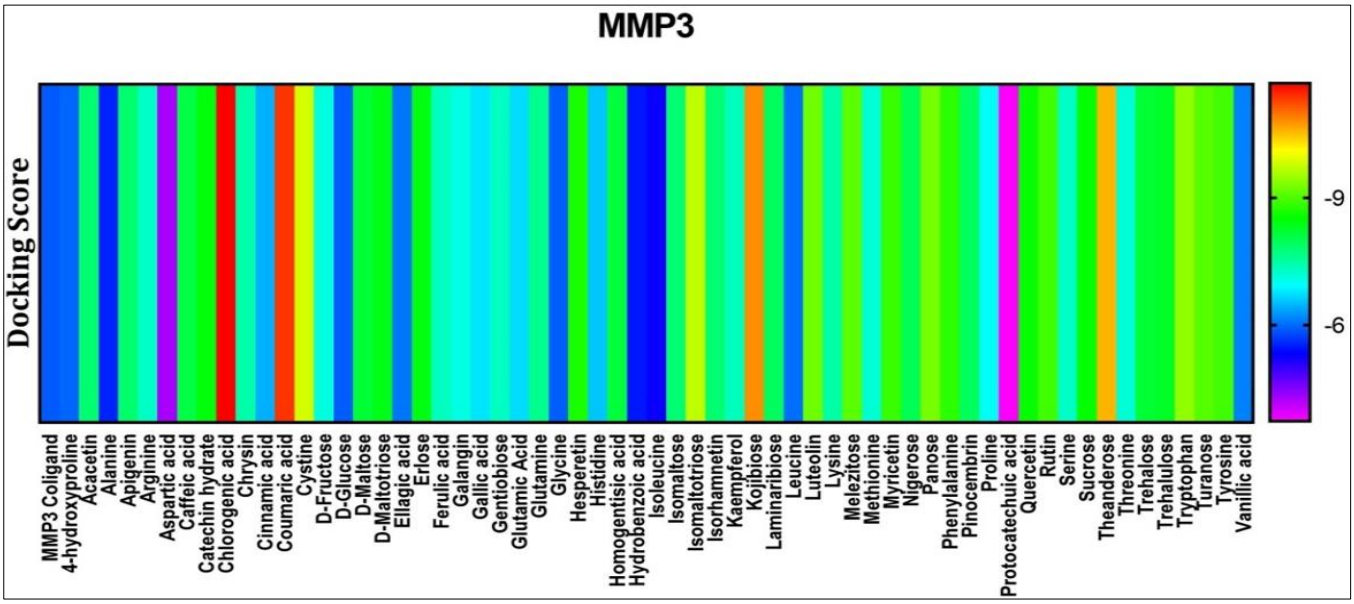

Fig 4: Heat map representation of docking result for compound interaction with the catalytic domain of Human hydrolase matrix metalloproteinase-3 (MMP-3) complex The free energy binding of phytochemicals of *A. mellifera* docked into the substrate binding site of Hydrolase matrix metalloproteinase-3 (MMP-3) complex, compared with the antagonist, NNGH and represented as heat map. (The scale is a spectrum from purple (-3 kcal/mol) to red (-11 kcal/mol).

Heat map representation of docking result for compound interaction with the catalytic domain of Human hydrolase matrix metalloproteinase-9 (MMP-9) complex

Docking results here showed that compounds such as; Chlorogenic acid, erlose and rutin, look to have high affinity for the the catalytic domain of Human hydrolase matrix metalloproteinase-9 (MMP-9) complex. Upon antagonism, they may well be good potential drugs that may act via this mechanism

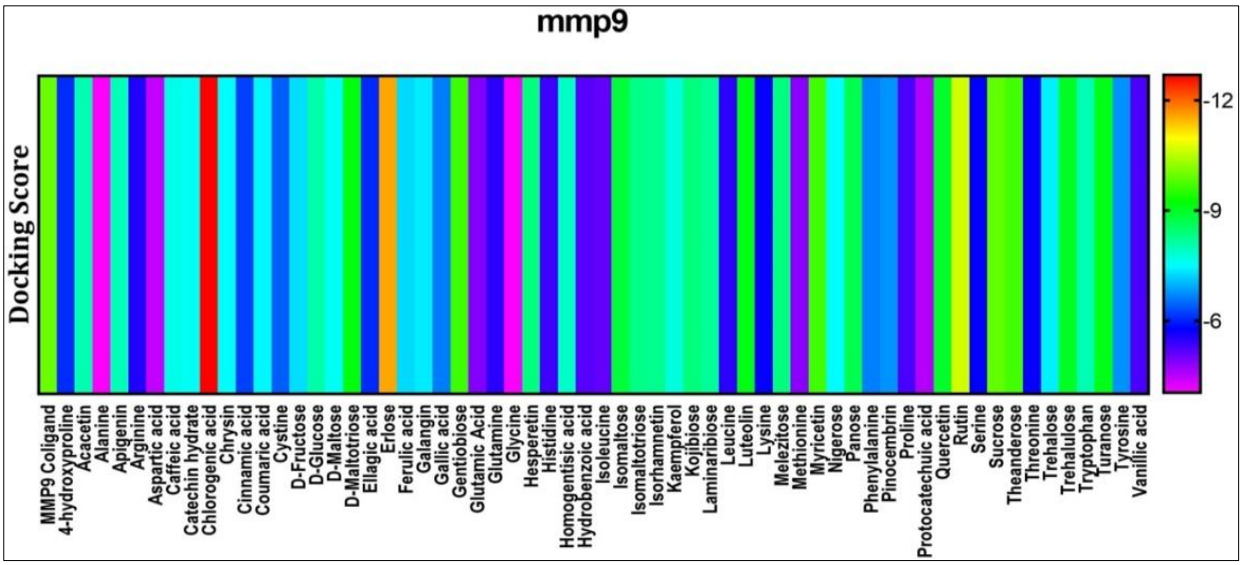

Fig 5: Heat map representation of docking result for compound interaction with the catalytic domain of Human hydrolase matrix metalloproteinase-9 (MMP-9) complex The free energy binding of phytochemicals of *A. mellifera* docked into the substrate binding domain of Hydrolase matrix metalloproteinase-9 (MMP-9) complex, compared with the antagonist, BE4 and represented as heat map. (The scale is a spectrum from purple (-4 kcal/mol) to red (-12 kcal/mol).

Heat map representation of docking result for compound interaction with the catalytic domain of human monoamine oxidase B.

Docking results here showed that compounds such as; Chlorogenic acid, erlose, D-maltotriose, Melezitose, Theanderose and Isomaltotriose, look to have high affinity for the the catalytic domain of human monoamine oxidase A. Therefore are likely to potentiate the antidepressant effect of honey via this mechanism.

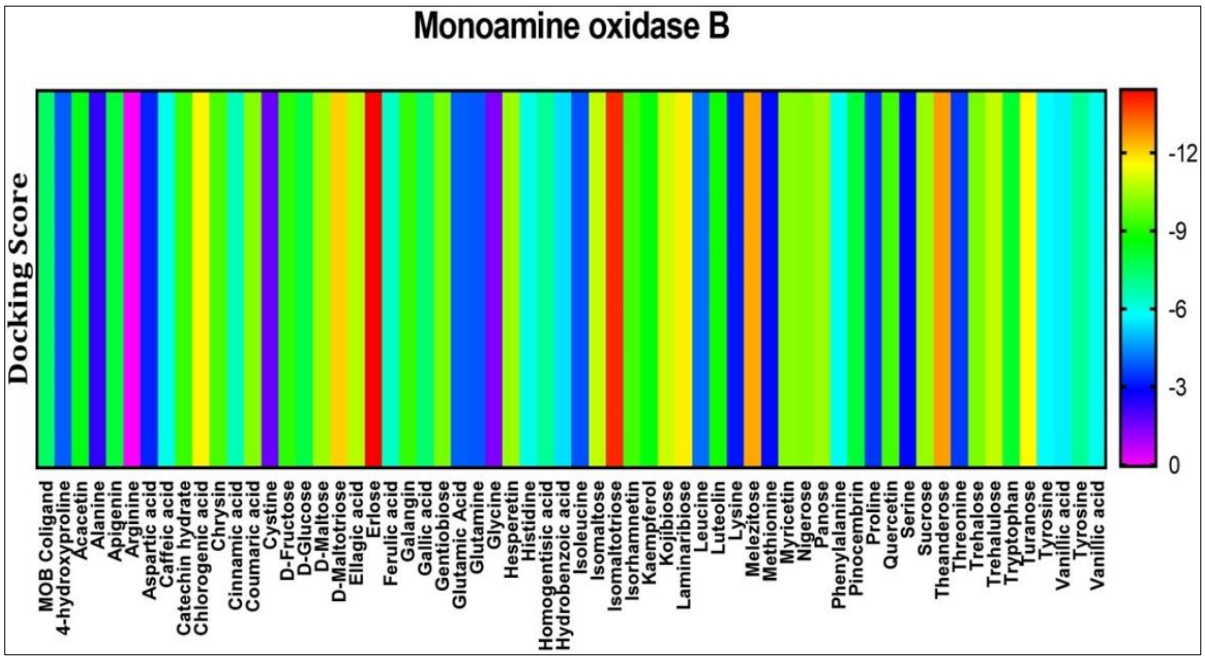

Fig 6: Heat map representation of docking result for compound interaction with the catalytic domain of human monoamine oxidase B. The free energy binding of phytochemicals of *A. mellifera* docked into the substrate binding, site of human monoamine oxidase B, compared with the antagonist, isathin and represented as heat map. (The scale is a spectrum from purple (-1 kcal/mol) to red (-13 kcal/mol).

Heat map representation of docking result for compound interaction with the catalytic domain of human monoamine oxidase A.

Docking results here showed that compounds such as; erlose, D-maltotriose, Melezitose, Theanderose, myricetin, and Isomaltotriose, look to have high affinity for the the catalytic domain of complex human monoamine oxidase A. Therefore are likely to potentiate the antidepressant effect of honey by inhibition of this enzyme.

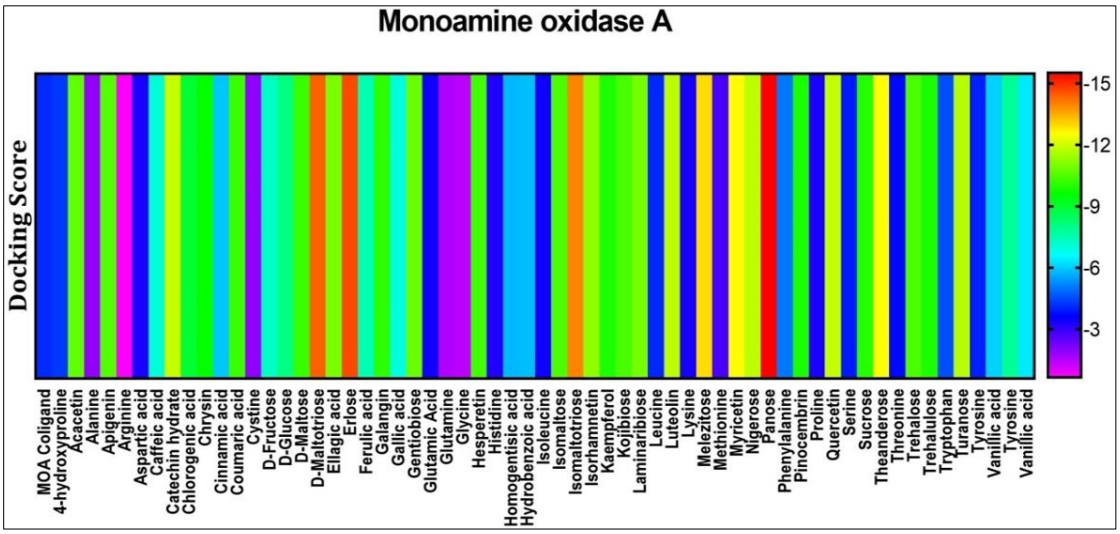

Fig 7: Heat map representation of docking result for compound interaction with catalytic domain of human monoamine oxidase A. The free energy binding of phytochemicals of *A. mellifera* docked into the substrate binding site of human monoamine oxidase A, compared with the antagonist, hamin and represented as heat map. (The scale is a spectrum from purple (-1 kcal/mol) to red (-15 kcal/mol).

Heat map representation of docking result for compound interaction with the catalytic domain of *Mus musculus* cyclooxygenase active site of COX-2

Docking results here showed that compounds such as; Chlorogenic acid, Trehalose, Kojibiose, nigerose, quercetrin, ellagic acid, gentiobiose, galandin, Melezitose, myricetin, and Isomaltotriose, look to have high affinity for the the catalytic domain of complex human monoamine oxidase A. Therefore are likely to potentiate the antidepressant effect of honey by inhibition of this enzyme.

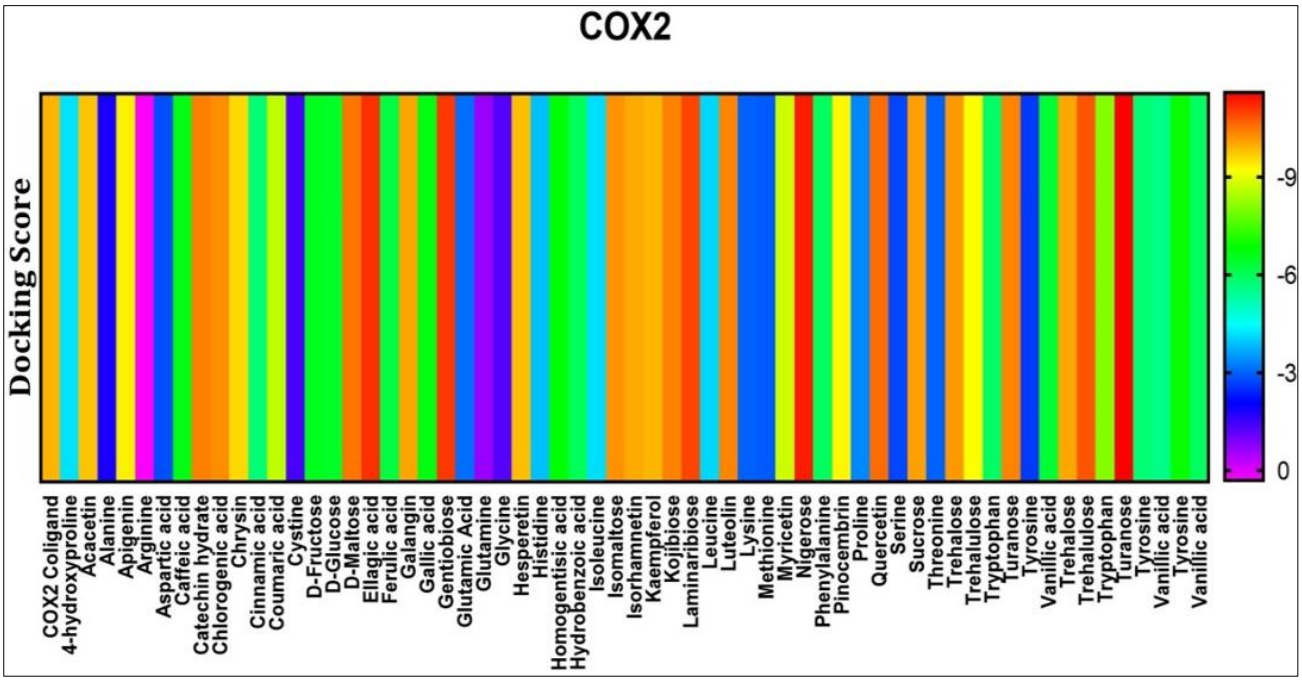

Fig 8: Heat map representation of docking result for compound interaction with the catalytic domain of *Mus musculus* cyclooxygenase active site of cox-2 The free energy binding of phytochemicals of *A. mellifera* docked into the substrate binding active site of cyclooxygenase 2 compared with the antagonist, diclofenac and represented as heat map. (The scale is a spectrum from purple (0 kcal/mol) to red (-10 kcal/mol).

Heat map representation of docking result for compound interaction with the catalytic domain of *Mus musculus* cyclooxygenase active site of cox-2

Docking results here showed that compounds such as; Kojibiose, theanderose, erlose and D-maltotriose, look to have high affinity for the the heme domain of Human endothelial nitric oxide synthase.

Therefore are likely to potentiate the antidepressant effect of honey by inhibition of this enzyme.

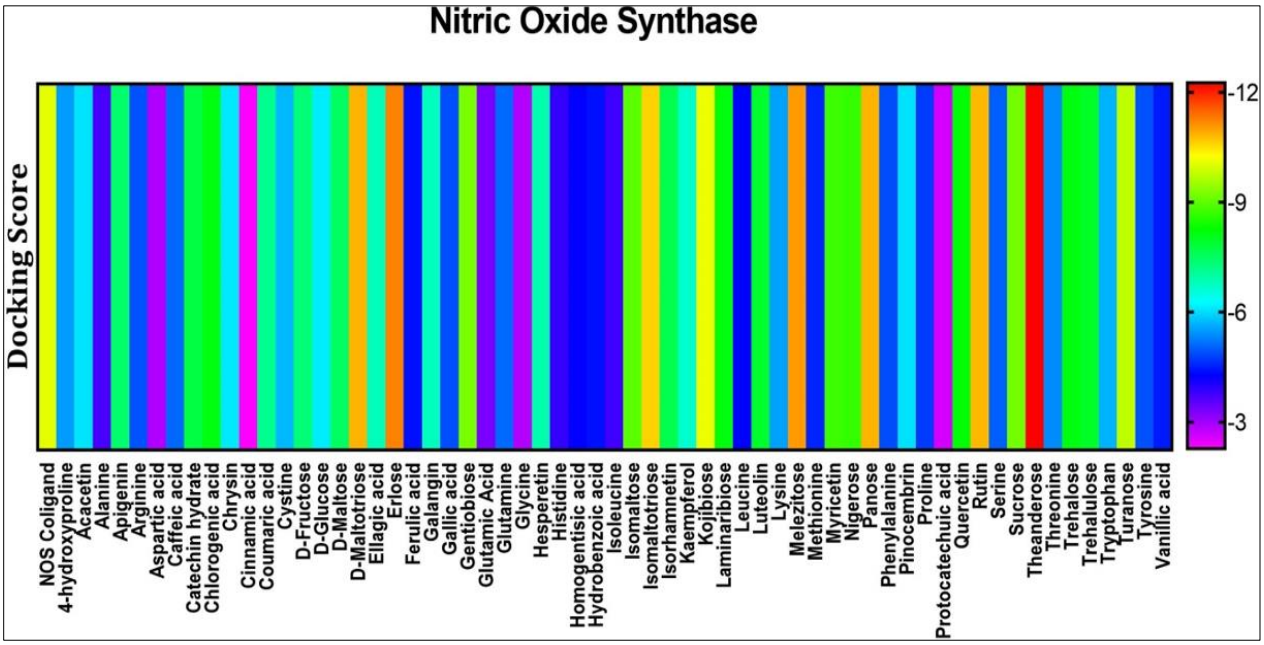

Fig 9: Heat map representation of docking result for compound interaction with heme domain of Human endothelial nitric oxide synthase. The free energy binding of phytochemicals of *A. mellifera* docked into the substrate binding site of Human indoleamine 2,3-dioxygenase 1 (IDO1), compared with the antagonist, 7-(3-(Aminomethyl)-4-(cyclopropylmethoxy)phenyl)-4ethylquinolin-2-amine and represented as heat map. (The scale is a spectrum from purple (-2 kcal/mol) to red (-12 kcal/mol).

Heat map representation of docking result for compound interaction with heme domain of Human Histone deacetylase 2.

Docking results here showed that compounds such as; Kojibiose and Panose look to have high affinity for the the heme domain of Human histone deacetylase. Therefore are likely to potentiate the antidepressant effect of honey by inhibition of this enzyme.

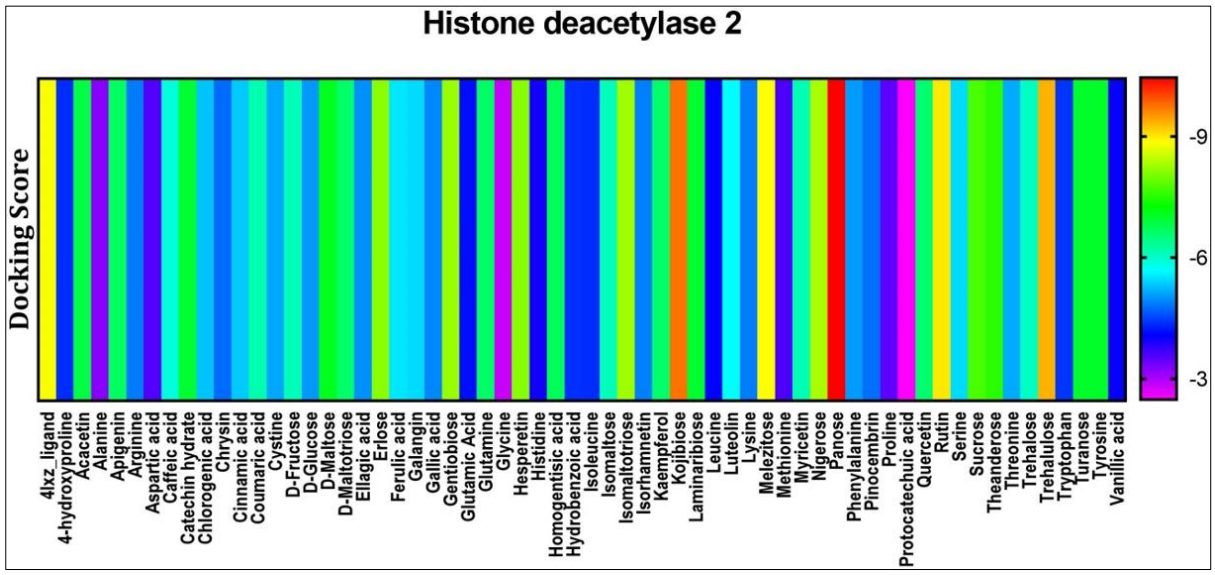

Fig 10: Heat map representation of docking result for compound interaction with heme domain of Human Histone deacetylase 2. The free energy binding of phytochemicals of *A. mellifera* docked into the substrate binding site of Human Histone deacetylase 2, compared with the antagonist and represented as heat map. (The scale is a spectrum from purple (-2 kcal/mol) to red (-10 kcal/mol).

Pharmacokinetic/toxicological properties of compounds present in *A. mellifera*

According to the Lipinski's rule of five, a good potential oral drug is not expected to violate more than two of the 4 laws (Lipinski, 2001) [14]. D-Maltotriose, Erlose, Isomaltotriose, Melezitose, Rutin, Panose and Theanderose look to have high affinity for some of the targets of concern, but the violate the law of potential oral drug candidature. chlorogenic acid, nigerose, myricetin coumaric acid also demonstrated high affinity for various targets. Hence, are likely to be investigated as oral antidepressant agents.

Table 1: showing the pharmacokinetic/toxicological properties of compounds present in *A. mellifera*

Compounds	Mol MW	Donor HB	Accpt HB	Qplog Po/W	HOA	ROF
4-hydroxyproline	131.131	3	5.2	-2.871	2	0
Acacetin	284.268	1	3.75	2.463	3	0
Alanine	89.094	3	3	-2.959	2	0
Apigenin	270.241	2	3.75	1.607	3	0
Arginine	174.202	7	5	-3.529	1	1
Aspartic acid	133.104	3	4	-3.886	1	0
Caffeic acid	180.16	3	3.5	0.545	2	0
Catechin hydrate	290.272	5	5.45	0.449	2	0
Chlorogenic acid	354.313	6	9.65	-0.27	1	1
Chrysin	254.242	1	3	2.349	3	0
Cinnamic acid	148.161	1	2	1.897	3	0
Coumaric acid	326.302	5	11.25	-0.577	2	0
Cystine	240.292	6	7	-3.164	1	1
D-Fructose	180.157	5	8.3	-1.696	2	0
D-Glucose	180.157	5	10.2	-2.265	2	0
D-Maltose	342.299	8	18.7	-3.62	1	2
D-Maltotriose	504.441	11	27.2	-5.521	1	3
Ellagic acid	302.197	4	8	-1.294	2	0
Erlose	504.441	11	25.3	-5.204	1	3
Ferulic acid	194.187	2	3.5	1.371	3	0
Galangin	270.241	2	3.75	1.778	3	0
Gallic acid	170.121	4	4.25	-0.578	2	0
Gentiobiose	342.299	8	18.7	-4.138	1	2
Glutamic Acid	147.13	4	5	-3.015	1	0
Glutamine	146.146	5	5.5	-4.196	1	0
Glycine	75.067	3	3	-3.004	1	0
Hesperetin	302.283	2	4.75	1.782	3	0
Histidine	155.156	4	5	-2.679	2	0
Homogentisic acid	168.149	3	3.5	0.407	2	0
Hydrobenzoic acid	183.12	2	3.75	0.101	2	0
Isoleucine	131.174	3	3	-1.524	2	0
Isomaltose	342.299	8	18.7	-4.007	1	2
Isomaltotriose	504.441	11	27.2	-5.709	1	3
Isorhamnetin	316.267	3	5.25	1.2	3	0
Kaempferol	286.24	3	4.5	1.042	3	0
Kojibiose	342.299	7	18	-3.83	1	2
Laminaribiose	342.299	8	18.7	-3.898	1	2
Leucine	131.174	3	3	-1.521	2	0
Luteolin	286.24	3	4.5	0.927	3	0
Lysine	146.189	5	4	-3.187	1	0
Melezitose	504.441	11	25.3	-5.076	1	3
Methionine	149.207	3	3.5	-1.588	2	0
Myricetin	318.239	5	6	-0.298	2	1
Nigerose	342.299	8	18.7	-3.458	1	2
Panose	504.441	10	26.5	-5.415	1	3
Phenylalanine	165.191	3	3	-1.145	2	0
Pinocembrin	256.257	1	3.25	2.358	3	0
Proline	115.132	2	3.5	-2.089	2	0
Protocatechuic acid	496.908	0	3.7	8.111	1	1
Quercetin	302.24	4	5.25	0.368	2	0
Rutin	610.524	9	20.55	-2.582	1	3
Serine	105.093	3	3.7	-3.314	1	0
Sucrose	342.299	8	16.8	-3.681	1	2
Theanderose	504.441	11	25.3	-4.871	1	3
Threonine	119.12	3	3.7	-3.35	1	0

Trehalose	342.299	8	18.7	-3.868	1	2
Trehalulose	342.299	8	16.8	-3.376	1	2
Tryptophan	204.228	4	3	-1.06	2	0
Turanose	342.299	7	18	-3.696	1	2
Tyrosine	181.191	4	3.75	-1.866	2	0
Vanillic acid	168.149	2	3.5	1.042	2	0
1HOV Coligand	574.734	3	14.9	1.434	2	1
1OJA Coligand	147.133	1	4.5	0.118	2	0
1PXX Coligand	296.152	2	2.5	4.505	3	0
2Z5X Coligand	212.251	1	1.75	3.062	3	0
4G9L Coligand	316.371	2	9.45	-0.094	3	0
6ESM Coligand	422.495	2	4.75	5.5	2	1
6PP1 Coligand	333.432	4	3.25	3.281	3	0
4LXZ Coligand	264.324	3	6.7	0.746	3	0

Mol wt_MW,: R.V.: 130–725; donorHB, estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution: R.V.: 0.0–6.0; accptHB, estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution: R.V. = 2.0–20.0; QPlogPo/w, predicted octanol/water partition coefficient: HOA, human oral absorption level, 1, 2, 3: 1 = low, 2 = medium; ROF, the number of violations of Lipinski's rule of five;

Discussion

Depression is a mood disorder that involves a constant feeling of sadness and loss of interest. It is a known mental disorder shown by many studies. In most cases, depression can lead to suicide or unintentional hurting of oneself (Wilcox. *et al.,* 2004) [32]. Depression is considered as an imbalance of neurotransmitters and the production of the neurotransmitters catalysed by various enzymes directly or indirectly. It be should understood that depression affects every person in a unique way. The following enzymes; Monoamine oxidase A and B, Cyclooxygenase-2, Matrix Metalloproteinase 2, 3, 9, Histone deacetylase 2 and Nitric oxide synthase have shown to be implicated in the mechanisms of depression and these enzymes were docked with the phytochemical compounds of honey obtained from literature as described by Ehigiator *et al*. (2021). Some plants have been implicated in amelioration of depression. previous studies have identified the use of honey in the treatment of depression (Mijanur *et al.,* 2014) [15]. Investigation of the antidepressant effect of honey (*Apis mellifera*) was carried out, using *in-vivo* pharmacological evaluations (tail suspension test and forced swim test) *in-silico* studies was employed to predict the likely mechanism of action. In tail suspension and forced swim tests, immobility study, it was observed that honey may remedy conditions of depression but was more likely to have a potent a synergistic effect with imipramine. Both tests were positive and it was imperative to attempt to further investigate the probable mechanism of action of honey in depression, using the phytochemicals of honey obtained through literature mining to dock with the enzymes involved in depression, hence molecular docking was involved. Molecular docking research focuses on computationally simulating the molecular recognition process; it aims to achieve an optimized conformation for both the protein and ligand such that the free energy of the overall system is minimized. Chlorogenic acid and Coumaric acid were found to have good docking scores with the matrix metalloproteinases MMPs.Chlorogenic acid seemed to have potential inhibitory affinity for MAO-B while, myricetin, catachin hydrate, isohamnetin, luteolin, quercetin presented with potential inhibitory affinities for MAO-A. MAO-A mainly metabolizes 5-HT, dopamine (DA) and norepinephrine (NE) Chaurasiya *et al.,* 2014; Sacher *et al.,* 2011) [5, 24].

Ellagic acid was the only compound with good potential inhibitory effect on COX-2, upon docking. COX-2 is inducible, short-lived and is responsible for the biosynthesis of prostaglandins in inflammatory cells and CNS. COX-2 is known to interact with neurotransmitters such as acetylcholine, serotonin, and glutamate. COX-2 contributes to the pathogenesis of the depressive disorder. (Peskar 2001; Müller *et al.,* 2009) [21, 18]. A previous study on the antidepressant activity of honey mixed barely resulted to a significant decrease on depression, stress, and mood disturbances scores compared with the control group when used on elderly depressed patient. Nevertheless participants reported that they observed improvements 3-4 days after the initiation of the initiation of treatment (Amira and Amin 2018). It is pertinent to also note that, in as much as compounds like D-Maltotriose, Erlose, Isomaltotriose, Melezitose, Rutin, Panose and Theanderose look to have high affinity for some of the targets of concern, they may not pass as good oral drugs as they violate the rule of five. However, compounds such as; chlorogenic acid, nigerose, myricetin coumaric acid demonstrated high affinity for various targets and do not violate the rule of potential oral drug (Lipinski, 2001) [4]. Hence, are likely to be investigated as oral antidepressant agents.

Conclusion

This study demonstrated that honey has a promising antidepressant activity, with a strong synergistic effect with imipramine. Further preclinical studies on confident in safety should be investigated with other derivatives like propolis, for drug discovery and eventual clinical trials investigation within the respect of antidepressant activity and synergistic effect of honey with imipramine. Furthermore chlorogenic acid which is found to be the most isolated compound that shows some affinity for inhibitory potential on more enzymes involved in depression should be properly be investigated as a likely antidepressant hit target agent.

Conflict of Interest

The authors declare no conflict of interest.

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