



Research Article

## Exploring the Potential of Honey and Curcumin as Antidepressant

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### Article History

Received: September 24, 2018

Revised: March 10, 2019

Accepted: June 03, 2019

Published: June 26, 2019

### Authors' Contributions

MNS identified the research area, prepared and conducted the research. HR and KA assisted in provision of research material. MNR helped in experiments and writing the manuscript. MRT assisten in designing the project. AM helped in sampling.

### Keywords

Antidepressant, Honey, Therapeutic, Rat model, Curcumin

**Abstract** | Depression is a common psychiatric disorder which is characterized by mood swings, aversion from activity and apathy which affects the thoughts, behavior and feelings of wellbeing. Honey and curcumin, traditional folk medicines, are thought to steadfast the defense mechanisms of body against oxidative stress which is a key factor in elevating depression. This study is designed to reveal the efficacy of honey and curcumin against depression in rat model. 24 male wister rats were randomly divided into 4 groups. After the trial, blood biochemistry was done in which antioxidant enzymes like SOD, Catalyze, Glutathione peroxidase were performed that shows significantly high levels in the blood than the group that was treated with nicotine and shows a positive correlation with the days at which the rat's groups were given a supplemented feed. Total antioxidant capacity and antioxidative stress shows significant results by the selected treatment.

**To cite this article:** Sheas, M.N., Rasool, H., Rafique, M.N., Tariq, M.R., Muhammad, A. and Ali, K., 2019. Exploring the potential of honey and curcumin as antidepressant. *Punjab Univ. J. Zool.*, 34(1): 89-95. <http://dx.doi.org/10.17582/journal.pujz/2019.34.1.89.95>

## Introduction

Depression is front runner causative agent of disability in major populations. WHO (World Health Organization) has stated that depression now standing at 4<sup>th</sup> place will be the 2<sup>nd</sup> most cause of the disability in world by 2020 (Kessler *et al.*, 2013). Pakistan is not an exception with 25-72 % prevalence in women and 10-44 % in men (Husain *et al.*, 2000). Women in Pakistan as well as globally shares the double burden of this disease overall. Hospital based surveys have also revealed increased incidence of depression

among women with share of 60-70% among total hospitalized patients (Ali *et al.*, 1993). For centuries, depression was treated with herbal ailments having strong pharmacotherapeutic effects. Curcumin falls under the category of plantsis a bright orange-yellow color pigment of turmeric having proved pharmacological significance against oxidants, microbes, neurodegenerators, immunomodulators and pro-inflammatory and pro-depressive agents (Yu *et al.*, 2013). Disruption of monoaminergic amines which causes neurotransmission, particularly the availability of serotonin, were formerly speculated as the basic source which leads to major depression (Cowen, 2008). These comprise activation of immuneinflammatory pathways, imbalance in the HPA (High Physical Activity) axis, neuroprogression, nitrosative stress, dysfunctioning of mito-

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chondria and increased oxidative stress (Leonard, 2012) resultantly, this has increased the attention in compounds or components that effect these pathways. For examples the treatments which involves anti-inflammatory mechanism anti-inflammatory treatments consequence in immuno-inflammation like aspirin, cyclo-oxygenase-2 inhibitors, tetracycline and polyunsaturated fatty acids (Berk *et al.*, 2013; Fond *et al.*, 2014). Antioxidant therapies that improve defense system by lowering damages done by free radicals as by using Ebselen, coenzyme-Q10, tocopherols, n-acetyl, sulfur containing cysteine amino acid and (Berk *et al.*, 2013; Scapagnini *et al.*, 2012). Fascinatingly, pharmaceutical depression suppressing drugs formerly presaged for influencing the action of monoaminergic amines, evidences also shown that these monoaminergic amines can improve neurotrophic factors, modify immuno-inflammations, decrease stress induced because of oxidation, and effect the HPA activity (Hannestad *et al.*, 2011).

Honey is viscid sticky secretion which is sweet in nature manufactured by the honey bees by the transformation of nectar from flowers or other plant secretions. Honey has a vital composition, it is an excellent source of numerous components primarily water and carbohydrates (sugars) which are about 17.2% and 79.6% respectively. Similarly percentage of dextrose and laevulose in honey are 31.28% and 38.19% respectively whereas honey also contains 7.3% maltose and 1.3% % sucrose. Honey also contains 0.57% acids, 0.266% proteins, 0.043% nitrogen, 0.1% amino acids, a minute quantity of minerals which is about 0.17% and 2.2% of honey includes a lot of other components such as aroma substances, flavors, collides, pigments, sugar alcohols, phenolics and vitamins (Todd *et al.*, 2008). Honey is a natural food product deprived of all side effects which are detrimental to human health. There are numerous components in honey which have antioxidant potential like phenolic compounds, Vitamin C and antioxidant enzymes (peroxidases, catalases etc.). High value of these components in honey ensures the presence of antioxidants in honey in large amount. This high antioxidant potential in honey works against depression during increased psychological, mental and physical stress (Jaganathan *et al.*, 2009). Honey's sugars has been utilized in traditional medicines (folk medicines) since antiquity as well as in current times. In apitherapy, honey is extensively used because of its importance in the treatment of infected wounds, asthma, skin ulcers, burns and gastrointestinal tract (GIT) disorders (Akanmu *et al.*, 2011). Curcumin is a dynamic segment in *Curcuma longa* (Zingiberaceae), well known as Asian yellow zest, has found to have massive therapeutic potential as autoxidation, antimicrobial, quieting, liver protective, and anticancer. Control in Neurodegenerative diseases and neuroprotective effects are enhanced by the use of curcumin studied in the animal efficacy studies (Syed *et al.*, 2007). Pakistan in like manner has a bit of the most essential infant tyke and maternal

passing rates on the planet (Patel *et al.*, 2007) which influences enthusiastic health. Curcumin is a dynamic settling in *Curcuma longa* Linn (Zingiberaceae), more routinely known as the Asian yellow flavor, has found to have tremendous healing potential as cancer prevention agent, antimicrobial, calming, hepatoprotective, and anticancer. Curcumin in like manner has neuroprotective potential against a significant measure of neurodegenerative issue in animal models (Patel *et al.*, 2007). Keeping in view the benefits of honey and curcumin this study was planned to ascertain its potential in reducing the symptoms associated with depression in rat model.

## Materials and Methods

### *Procurement of raw material*

The current study was conducted in the National Institute of Food Science and Technology, University of Agriculture, Faisalabad. For this purpose, rhizome of honey and curcumin was acquired from local market of Faisalabad while rats (8-12 weeks' ages) were purchased from National Institute of Health Islamabad.

### *Determination of total phenolic content (TPC), free radical scavenging activity (DPPH assay), ferric Reducing/Antioxidant Power Assay (FRAP) and thiobarbituric acid reactive substances (TBARS)*

The antioxidant contents of honey and curcumin samples were estimated by following the Folin-Ciocalteu method (FCM) as described in Senevirathne *et al.* (2006). 2,2-diphenyl-1-picrylhydrazyl (DPPH) was assayed to ascertain the antioxidant potential of turmeric extract samples as explained by Isla *et al.* (2011). Ferric Reducing/Antioxidant Power Assay (FRAP) was determined by the method described by Benzie and Strain (1996). Thiobarbituric Acid Reactive Substances (TBARS) were analysed by following the method stated by Asghar *et al.* (1989). The standard curve was organized utilizing malondialdehyde (MDA) and TBARS were stated as milligram MDA/kilogram of sample. Oxidation of lipid was measured as TBARS value by using formula.

### *Experimental animal model*

Experimental model for this study was designed to ascertain the ameliorative role of honey and curcumin against depression. For study to start, 24 *spraguedawley* rats were housed in animal room of University of Agriculture, Faisalabad. Rats were acclimatized for a period of one week on normal diet and free access to water.

### *Experimental protocol*

A total of 24 rats were recruited for this research based trial which were accustomed over normal diet and unrestricted access to water for one week before starting trial. After one week four groups were constituted having 6

rats in each group:  $G_0$ ,  $G_1$ ,  $G_2$  and  $G_3$  (Table 1).  $G_0$  acted as negative control group as it was feed with normal diet and no smoke treatment.  $G_1$  served as positive control group given smoke treatment with no therapeutic treatment.  $G_2$  was feed on normal diet supplemented with honey and curcumin while  $G_3$  was given antidepressant medicine supplemented in normal diet

**Table 1: Experimental study design.**

Groups	Description	Treatments
$G_0$	Negative control	Normal Diet
$G_1$	Positive control	Nicotine induced rats on normal diet
$G_2$	Treatment 1	Nicotine induced rats on Honey + Curcumin+ normal diet
$G_3$	Treatment 2	Standard antidepressant (Floxacin) + normal diet

#### Induction of depression

Nicotine (12mg/cigarette) was incorporated as a depression escalating tool in the trial as rats were treated with smoke containing nicotine in an enclosed glass jar. The procedure was operated as described by Hu *et al.* (2013), which is used with little modifications in nicotine exposure time and amount of nicotine.

#### Cigarette smoke inhalation exposure system

The Teague model TE-10C was incorporated in the study trial. This microprocessor precisely controlled the smoke levels inside glass jar having experimental rats. Height, weight, and width of the inhalation chambers was 28, 24 and 25 inches, respectively. Sidestream or mainstream smoke was introduced in the glass jar, but sometimes as the conditions demanded combination of both of them were utilized. Marlboro Red Class cigarettes were used to produce both sidestream and mainstream smoke for inducing depression by active smoking in rats. While, passive smoking environment was created by sidestream production of smoke. FTC (Federal Trade Commission) methodology was brought into use to smoke the cigarettes to the rats. According to FTC method 35 cm<sup>3</sup> puff of cigarette for 2 seconds and nine puffs/minute (Teague *et al.*, 1994).

#### Assessment of depression

Self-induced depression was measured using behavioral examination technique as explained by Sun *et al.* (2017).

#### Biological evaluation

At the end of this anti-depressant ascertaining trial of honey and curcumin, samples from blood were drawn by 22G needle to assess following parameters:

#### Assessment of total antioxidant status and total antioxidant capacity (TAC)

Glutathione peroxidase, catalase and superoxide dismutase were assessed for examining the antioxidant potential (Reddy *et al.*, 2011). Methodology described by Erel (2004) was incorporated to testify the TAC of serum.

#### Forced Swim Test (FST)

FST is considered a standard technique for depression assessment, initially tested by Porsolt *et al.* (2011). After self-induced depression in Spraguedawley rats they were shifted to FST room for 30 minutes before actual test procedure was performed. A pre-swim test for 15 minutes was used to acclimatize the rats with the prevailing conditions of temperature (22°C) and water depth of 30 cm. Light source was kept dim to avoid any anxiety or irritation and video was recorded for data analysis on software. Rats were forced to swim for a total of 6 minutes in the same circumstances as in pre-swim test. A trained observer who was uninformed about treatment given to rats, recorded cumulative immobility after 2 min. When the test conceded, rats were removed out of water and dried by placing paper towel over them for 30 minutes before placing them into their mother cage.

#### Statistical analysis

Statistical analysis was conducted by applying two factor factorial according to the study design as explained by Montogemery (2008).

## Results and Discussion

#### Antioxidant potential of curcumin and honey

Mean values for curcumin and honey are shown in Table 1. It is obvious from the tabulated values that the natural curcumin and honey has antioxidant capacity. As shown in the table values, obtained from analysis of curcumin were as mentioned. The mean values for FRAP in curcumin was 212.39 ±0.50, DPPH65.84±0.28, TPC1105.96±0.52, and TBAR were 5.44±0.13 that has significant effect as an antioxidant. Similarly Honey being a natural source and considered as best antioxidant having antioxidant capacity that are shown in mean values of honey for FRAP that was 82.52±0.57, DPPH 168.60±0.54, TPC 159.24±0.50 and TBAR 2.47±0.03 that shows highly significant capacity of honey to act as antioxidant against depression.

#### Total phenolic contents of honey and curcumin

Free radical scavenging and metal chelating activity is performed by the phenolic compounds present in the natural food. These findings are quiet resembling to the results of TPC given by the different scientists. Mansouri *et al.* (2012) reported the total phenolic capacity of honey that is quiet near to the findings in the Table 1. In the present study, the TPC of honey samples was in the narrow range



from 110.394 to 196.500mg GAE/100g honey.

The TPC results were compared with some other honey types according to the scientist that is quiet resembling to the honey values. Total phenol was compared to the TPC values that is total phenol was also compared to the TPC value reported for the similar type of honey from different countries. It was higher TPC value (159.20mg-GAE/100g honey) with respect to the honey from different areas of Pakistan.

In our study the results related to total phenolic contents of honey are high and maximum value was 159mg-GAE/100g honey as compared to the study in which different contents of TPC were determined like Indian honey has (47 to 98mgGAE/100g honey) the honey is high then another type of honey is Argentina north west honey that has range about 18.70 to 107.23 mg/GAE/100mg honey. So significant results shows that honey has high antioxidant power because of containing high total phenolic content.

#### *Free radical scavenging antioxidant power*

The significant values of free radical scavenging activity in curcumin was determined as 168.20 and shown in the Table 2. The normal range for the depth activity varies from the 160 to 170 that shows significant effect of the curcumin in relation to honey. Honey and curcumin being natural has two times more power than the fluoxetine compounds. Some differentiation has been seen in honey samples even purchased from the same shop but have different scavenging capacity. In a study it is also proven that  $EC_{50}$  value of ascorbic acid was lower than other honey samples. In another study the free radicals scavenging activity of honey was found higher, the high activity of the honey and curcumin also depends on their origin and from the family which they belong, different types of honey and curcumin effects their antioxidant capacity.

#### *Thiobarbituric acid reactive substances (TBARS).*

Lipid stability test is used to measure malondialdehyde compounds that accelerates during auto-oxidation process and cause a release of free fatty acids or free radicals. Higher malondialdehyde content means more free reactive species are there. It is clear from the tables the values of TBAR is in the range of normal malondialdehyde values in honey and curcumin. The curcumin and honey yielded significantly lower values of MDA (9.77nmol malondialdehyde/mg) as shown in the Table 2.

#### *Ferric reducing antioxidant power (FRAP)*

The statistical results shown that ferrous chelating activity of curcumin and honey was significant as these have high chelation of ferrous ion. The values that obtained after evaluation the ferrous chelating effect of curcumin that is 212 and in honey it is 82 mgTE/100g of honey as men-

tioned in Table 4 and Table 2 respectively. So the higher the antioxidant power of curcumin is due to the presence of high phenolic contents in it that chelated the ferrous ions. Ferric reducing power of honey is high but combination of both curcumin and honey possess more ferric reducing capacity. Honey also seems an oxidation reduction component to control the oxidative damage compared to other synthetic components. It has been found that the total polyphenolic content and the  $Fe^{2+}$  content formed in the presence of the honey antioxidants are significantly correlated.

In a study different types of honey is evaluated for their antioxidant activity that shows that acacia honey has higher values than amber honey. Honey and curcumin have a high antioxidant power in terms of ferric reducing mechanism. Anti-oxidative mechanism is due to the action of reductions on breaking of free radical chains results in donation of hydrogen.

The reducing power of curcumin and honey has direct relationship with electron sharing ability, so the reducing power of a compound cinders a significant tool to perform antioxidant activity. By comparing the methods for the antioxidants as TPC that is strongly correlated to the FRAP contents value. Total phenolic content (TPC) is a different in mechanism than DPPH with different scavenging activity. There are some other constituents in honey also which also act as free radical scavengers but phenolic compounds of curcumin have high power to reduce the oxidative damage.

**Table 2: Mean values for antioxidants in honey and curcumin samples.**

Sample	FRAP mgTE/ 100g	DPPH mgAAE/ 100g	TPC (mgGAE/ 100g)	TBAR (malondial- dehyde/mg)
Honey	82.52 ± 0.37	168.60± 0.34	159.24± 0.30	2.47± 0.03
Curcumin	212.39± 0.50	65.84± 0.28	1105.96± 0.52	5.44± 0.13

#### *Antioxidant enzymes*

##### *Superoxide dismutase (SOD)*

Mean values that are shown in the Table 3 concludes a significant increase in the mean values of group ( $G_2$ ) honey and curcumin showing the highest value for the superoxide dismutase enzyme ( $G_2=3.3000$ ) while the lowest mean value is shown in the group ( $G_1= 2.4467$ ) stress induced following the group ( $G_3$ ) with synthetic antioxidant (fluoxetine) shows the superoxide dismutase enzyme activity about ( $G_3=2.8050$ ). The highest value of SOD was shown in the negative control group ( $G_0$ ) which was not induced with depression and was provided with normal diet is ( $G_0=2.9467$ ). Value of  $G_2$  is quite comparable with

G<sub>0</sub> Wang *et al.* (2009) discussed the results of curcumin that increases the level of SOD antioxidant enzyme in blood serum that further helpful in enhancing the potential of mitochondrial membranes from the oxidative stress. Imbalance of Mitochondrial membrane function (Wang *et al.*, 2009). Reactive oxygen species and increase in oxidative stress is also an outcome of the neurotoxin in the blood.

**Table 3: Mean antioxidant enzymes superoxide dismutase (sod= iμ/ml) in blood serum.**

Groups	Days	
	7	21
G <sub>0</sub>	2.9533b	2.9467b
G <sub>1</sub>	2.4867d	2.4467d
G <sub>2</sub>	2.5467cd	3.3000a
G <sub>3</sub>	2.6300cd	2.8050bc

*Glutathione peroxidase (GPx)*

GPx level when compared with the control as shown in Table 4. The significant increase in the mean values of group (G<sub>2</sub>) treated with honey & curcumin showing the highest value for the GPx enzyme (2676.0) while the lowest mean value is shown in the group (G<sub>1</sub>= 1777.3) stressed induced following the group (G<sub>3</sub>) with synthetic antioxidant shows the GPx enzyme activity about (2412.0). The highest values shown in the group of control group with normal diet and without stress induction that is (G<sub>0</sub>= 2673.0) maintains the body mechanism in the blood serum. The rats of negative control group G<sub>0</sub> which fed with a basic diet had normal Glutathione peroxidase (GPx) levels in the their blood serum but the levels of GPx was lower in those groups of rats that were stress induced by cigarette smoke (G<sub>1</sub>, G<sub>2</sub> and G<sub>3</sub>) as compared to G<sub>0</sub>. After treatment value of GPx in group G<sub>2</sub> was significantly increased as compared to both G<sub>1</sub> and G<sub>3</sub>. So combined effect of curcumin and honey is more significant than the effect of Fluoxetine.

**Table 4: Mean antioxidant enzymes glutathione peroxidase (gpx= iμ/ml) in blood serum.**

Groups	Days	
	7	21
G <sub>0</sub>	2663.3	2673.0
G <sub>1</sub>	1780.0	1777.3
G <sub>2</sub>	1733.2	2676.0
G <sub>3</sub>	1767.7	2412.0

*Catalase (CAT)*

Regarding to the mean values are showed in the Table 5 the significant increase in the mean values of group (G<sub>2</sub>) honey and curcumin showing the highest value for the catalase enzyme (26.880) while the lowest mean value is

shown in the group (G<sub>1</sub>= 9.450) stressed induced following the group (G<sub>3</sub>) with synthetic antioxidant shows the catalase enzyme activity about 22.070. The highest values shown in the group of control group with normal diet and without stress induction. The catalase enzyme level is influenced by the treatments fed on rats groups. The catalase activity level is 2089.2 iμ/ml to 2698 iμ/ml during the experimental time. The highest catalyze activity is shown in group of rats fed on curcumin + honey that is 2204.6 iμ/ml followed by the fluoxetine 2089.8 iμ/ml and control group of rats that fed normal diets. Decreased antioxidant enzyme activity is shown in stressed induced group of rats in serum. A study shows that decreased level of catalase also shows the inefficient activity of toxic compounds of water in tissues that enhances NO level. The rats in group fed on (G<sub>0</sub>) control feed shows non-significant effect on the level of catalase during the experiment. A study by (Srilatha *et al.*, 2010) reported that activities of catalase and glutathione enzyme were significantly increased by supplementation of curcumin. Lipid peroxidation and oxidative stress leads to the neural degeneration that decreases the glutathione and catalase enzyme levels. Increased level of MDA may be results because of poor antioxidant capacity of compound or high level of MDA were in nicotine treated rats that shifts the delicate level of antioxidant enzymes.

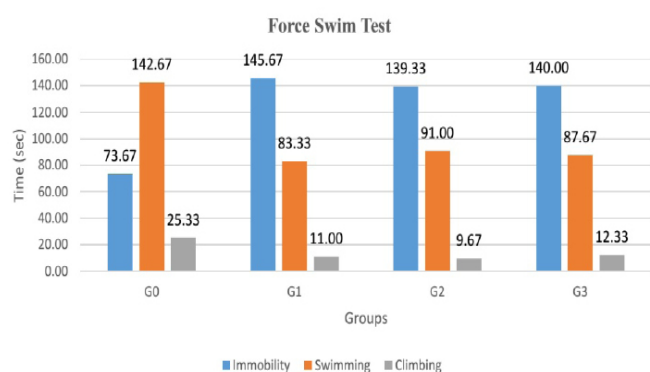
**Table 5: Mean antioxidant enzymes catalase (cat= iμ/ml) in blood serum.**

Groups	Days	
	7	21
G <sub>0</sub>	25.580a	25.473a
G <sub>1</sub>	9.490c	9.450c
G <sub>2</sub>	9.870c	26.880a
G <sub>3</sub>	9.387c	22.070b

*Forced Swim Test*

The graph presented the demographic values for the force swim test. The control group (g<sub>0</sub>) is negative control so, no stress would be induced that may leads to more activity factor in rats. So the time in which the rats of G<sub>0</sub> grouped covered the area in 140.67 sec. The group (G<sub>1</sub>) is a stressed induced group in which induction is done through smoke so swimming and climbing is less than control that covered area through swimming in about 80 sec and 20 sec. The (group G<sub>2</sub>) that is treated with supplemented feed with show high immobility and covered area at about 1545.6 sec and climbed for 11 sec. Rats shows immobility at 139.33 sec and swimming done at about 90 Sec and climbed for 9.67 seconds. The (group 3) rats containing synthetic anti-depressant covered the area by swimming at about 87.67 and climbing done at 12.33 and remain immobilize for 140 sec. The trial of animal model with forced swimming test shows the almost similar antidepressant like behavior but it shows improvement

in the swimming of the group which fed supplemented feed rather than fluoxetine. The findings were evaluated by the Yu *et al.* (2013) that the supplementation of rats with curcumin and honey shows significantly less immobilized time and increased the number of rotation in forced swim test.



**Figure 1: Force Swim Test for depression assesment.**

Curcumin and honey acts as a natural antidepressant that helps to identify the difference in the behavior of rats while climbing and swimming because of more neurotransmitters are involve in this mechanism that shows the anti-depressant activity. Curcumin with 100- 200mg/kg increased the activity in climbing and swimming in the mice. In previous studies by Xu *et al.* (2005) proved that increase in nor epinephrine, dopamine serotonin level increased in nerves that further increased time for both swimming and climbing behaviors in the forced swim test does It has been previously suggested by (Xu *et al.*, 2005). Curcumin antidepressant like activity is further supported by the increasing level of dopaminogenic activity that further inhibits the monoamine oxidase activity in the brain that mostly done by the presence of three important neurotransmitters that act like anti-depressant (Wang *et al.*, 2008).

## Conclusion and Recommendation

Depression is front runner causative agent of disability in major populations. Honey and curcumin can play an active role in reducing depression. The purpose of the research was to explore potential benefits of honey and curcumin against depression that is prevailing in Pakistan day by day. The curcumin is obtained by the turmeric that is further analyzed for their best antioxidant activities by adopting advance antioxidants test like FRAP, TBAR, DPPH and FRAP that shows highly significant ratios of polyphenols in the turmeric and honey by adopting the methods with some modifications. Animal efficacy study concluded that antioxidants enzymes shows significantly high ratios in the group treated with honey and curcumin and honey followed by the synthetic fluoxetine and a group that is stressed.

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