



NEUROPHARMACOLOGICAL EVALUATION OF AQUEOUS EXTRACTS OF FRUIT PEELS AND THEIR POLYHERBAL FORMULATION: ANTIDEPRESSANT AND MUSCLE RELAXANT POTENTIAL

MEYVE KABUKLARININ SULU EKSTRELERİ VE POLİBİTKİSEL FORMÜLASYONUNUN NÖROFARMAKOLOJİK DEĞERLENDİRİLMESİ: ANTİDEPRESAN VE KAS GEVŞETME POTANSİYELİ

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ABSTRACT

Objective: This study aims to assess the neuropharmacological properties of peels from specific fruits, namely *Annona squamosa*, *Cucumis melo*, *Actinidia deliciosa*, *Malus pumila*.

Material and Method: Wistar albino rats (weighing 150 g), regardless of gender, were allocated into six groups for forced swim tests, locomotion assessments, and muscle coordination evaluations. Diazepam and imipramine were employed as reference standards. At doses of 200 and 400 mg/kg, all peel extracts showed a reduction in immobility time, improved rotarod performance, and a notable increase in locomotor activity.

Result and Discussion: The efficacy ranking for immobility time was as follows PHF>APMP>APCM>APAS>APAD. In terms of skeletal muscle relaxation, the order of effectiveness was: PHF>APCM>APMP>APAD>APAS and the treatment groups' locomotor activity followed this sequence: PHF>APMP>APCM>APAD>APAS. All the selected peel extracts exhibited noteworthy effects on immobility, locomotor activity, and muscle relaxation. However, a more comprehensive investigation is required to elucidate the precise mechanisms underlying the antidepressant effects of the selected peel extracts and PHF.

Keywords: Fruit peels, neurological activity, polyherbal mixture

ÖZ

Amaç: Bu çalışma, *Annona squamosa*, *Cucumis melo*, *Actinidia deliciosa*, *Malus pumila* gibi belirli meyvelerin kabuklarının nörofarmakolojik özelliklerini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Wistar albino sıçanlar (ağırlıkları 150 g) cinsiyete bakılmaksızın zorunlu yüzmeye testleri, hareket değerlendirmeleri ve kas koordinasyonu değerlendirmeleri için altı gruba ayrıldı. Referans standartlar olarak diazepam ve imipramin kullanıldı. 200 ve 400 mg/kg dozlarında, tüm kabuk ekstraktları hareketsizlik süresinde azalma, rotarod performansında iyileşme ve lokomotor aktivitede kayda değer bir artış gösterdi.

Sonuç ve Tartışma: Hareketsizlik süresine ilişkin etkinlik sıralaması şu şekildedir: PHF>APMP>APCM>APAS>APAD. İskelet kası gevşemesi açısından etkinlik sırası şu

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şekildeydi: PHF>APCM>APMP>APAD>APAS ve tedavi gruplarının lokomotor aktivitesi şu sırayı takip etti: PHF>APMP>APCM>APAD>APAS. Seçilen tüm kabuk özleri hareketsizlik, lokomotor aktivite ve kas üzerinde kayda değer etkiler sergiledi.

Anahtar Kelimeler: Meyve kabukları, nörolojik aktivite, polibitkisel karışım

INTRODUCTION

Oxidative stress poses a significant challenge to cells by inducing the production of reactive oxygen species (ROS) and antioxidants that influence signaling pathways. The byproducts of this process play a crucial role in brain pathology and function across various neurological conditions. Since oxidative stress is a primary therapeutic target in neurological diseases, it is essential to investigate diverse strategies that can effectively repair ROS-induced damage and address neurodegenerative disorders (NDDs) [1]. These conditions have been linked to the detrimental effects of free radicals and oxidative damage, which underlie the pathogenesis of several neurological diseases. Antioxidants, as free radical scavengers, hold the promise of preventing, delaying, or alleviating the burden of these disorders.

Free radicals are molecules with one or more unpaired electrons [2,3]. These radicals can cause various cellular alterations, such as DNA mutations, lipid peroxidation in cell membranes, changes in enzymatic activity, and even cell death [4]. Aerobic metabolism in the body produces oxygen free radicals, including hydroxyl radicals, superoxides, and reactive oxygen species (ROS) [5-7]. The excessive generation of free radicals can damage biomolecules like DNA, lipids, and proteins, increasing the risk of chronic diseases such as rheumatoid arthritis, cancer, diabetes, neurological disorders, and atherosclerosis [8]. Various neurological disorders are linked to oxidative injury or free radicals. Free radical scavengers are commonly used to prevent or delay neurological disorders by mechanisms such as scavenging activity, metal chelation, or inhibiting lipid peroxidation [9].

Antioxidants are natural compounds with low molecular weights, typically consisting of polyhydroxylated phenolic structures. These antioxidants include flavonoids, phenolic acids, tannins, lignans, stilbenes, catechins, and carotenoids, found in many fruits and vegetables. Certain cellular enzymes, located within specific cellular compartments, also exhibit strong antioxidant properties, neutralizing reactive radicals. By removing electrons or hydrogen atoms from substances, antioxidants can prevent oxidative damage within cells. The antioxidant activity is significantly influenced by the number and position of hydroxyl groups on their aromatic rings. Antioxidants act as scavengers of reactive radicals, mitigating the oxidative damage caused by reactive oxygen species (ROS), and can originate from either endogenous or exogenous sources [10,11].

In recent years, there has been a growing attention in exploring the antioxidant properties of phytoconstituents found in everyday food items like fruits and vegetables in particular. It is well-established that many of these phytochemicals, renowned for their antioxidant capabilities, are highly concentrated in the outer layers, such as peels. Regrettably, a substantial quantity of fruit and vegetable peels is discarded as waste, contributing to environmental challenges. Waste valorisation centers on transforming by-products or residues into valuable raw materials by using discarded items as energy sources or inputs in manufacturing. This process can also involve incorporating waste into final products. One common approach is recycling, where waste is recovered and repurposed into new, functional products. However, this often reduces the material's properties, leading to lower-quality applications, a process called downcycling. In contrast, upcycling enhances the value, quality, or functionality of waste materials, making it the preferred method for waste valorization [12-17].

Researchers uncover valuable bioactive compounds in these peels, demonstrating their potential health benefits, including antioxidative, anti-inflammatory, anti-cancer, antiviral, and cardio-protective activities, among others [18,19]. Numerous studies have consistently shown that the phenolic content in fruit peels often surpasses that found in the pulp [20].

Malus pumila (*M. pumila*) commonly referred to as the apple and belonging to the Rosaceae family, is renowned globally for its health-promoting attributes. Originally hailing from central Asia, the apple has now become a staple worldwide, with every part, including the skin, being edible.

Apples are rich in essential nutrients such as vitamin C, vitamin B12, calcium, phosphorous, and are a valuable source of carbohydrates [21]. The processing of canned apples and apple sauce generates apple peel waste, which, interestingly, has been found to be rich in polyphenols with demonstrated antioxidant and antiproliferative activities [22].

Annona squamosa (*A. squamosa*), a medium-sized tree belonging to the Annonaceae family, has a history of traditional use for its various parts, including fruits, seeds, leaves, and barks, to address a multitude of health issues [23]. Research on *A. squamosa* (*Custard apple*) peels has unveiled their antimicrobial and antioxidant properties [24].

Actinidia deliciosa (*A. deliciosa*), commonly known as kiwifruit and belonging to the Actinidiaceae family carries substantial global significance. Its fruits have been celebrated for their medicinal properties, containing phytoconstituents such as triterpenoids, flavonoids, phenylpropanoids, quinines, and steroids. Traditional Chinese medicine employs different parts of *A. deliciosa* to address various ailments, including hepatitis, pyorrhea, gingivitis, edema, rheumatoid arthritis, and various forms of cancer. Kiwi seeds are used as natural blood thinners, and kiwi fruit is a rich source of vitamins, often employed as a mild laxative [25,26].

Cucumis melo (*C. melo*) Linn, a member of the Cucurbitaceae family, is valued for different parts, including the pulp, root, seeds, and seed oil. It is associated with properties such as diuretic, emmenagogue, cooling, demulcent, aphrodisiac, galactagogue, and astringent. Over centuries, it has been used to treat kidney disorders, urinary tract issues, and various conditions like cough, bilious diseases, inflammation of the liver, liver and bile obstructions, eczema, and more [27]. Research has demonstrated the antioxidant potential of *C. melo* (musk melon) peels [28].

The current study investigates the CNS effects of aqueous peel extracts (AP) from *Malus pumila* (APMP), *Annona squamosa* (APAS), *Actinidia deliciosa* (APAD), and *Cucumis melo* (APCM). These peels utilized as a polyherbal formulation (PHF) and individually, were evaluated for their antidepressant and muscle relaxant potential. Additionally, the study sought to address the lack of research on fruit peel utilization for mood disorders, employing recognized experimental models and considering clinical relevance.

MATERIAL AND METHOD

Collection and Preparation of Peel Extracts

Fresh fruits were procured, and their peels were separated, cleaned, and shade-dried for one month. The dried peels were ground into a fine powder and extracted via cold maceration using water and ethanol (80:20). Extracts were concentrated, converted to powder, and stored for further use. A polyherbal formulation (PHF) was prepared by combining the extracts in equal proportions.

Preliminary Phytochemical Analysis

The aqueous peel extracts were tested for various phytochemicals using the standard preliminary phytochemical screening methods [29].

Dose Selection

Acute toxicity studies following OECD Guideline 423 confirmed safety up to 2000 mg/kg. Experimental doses of 200 mg/kg and 400 mg/kg were chosen, equivalent to 1/10th and 1/5th of the maximum non-toxic dose.

Experimental Animals

Male Wistar albino rats (180-200 g) were used. Gender differences were not assessed in this study due to resource constraints; however, future studies should include both sexes to ensure comprehensive results. Rats were acclimatized for two weeks before experiments.

Experimental Design

Rats were divided into 11 groups (n=6):

1. Control: Distilled water.
2. Standard: Imipramine (3 mg/kg).
- 3–10 Peel Extract Groups: Individual extracts at 200 mg/kg and 400 mg/kg.
3. PHF: 200 mg/kg.
4. The extracts were reconstituted in distilled water and administered orally to the animals using a calibrated gavage. The administration was performed once daily during the study period.

Experimental Models

Forced Swim Test (FST): To evaluate antidepressant activity. Immobility time was recorded during the last 4 min of a 6-min swim session.

Locomotor Activity: Assessed using an actophotometer to measure alertness.

Rotarod Test: Evaluated muscle coordination and relaxant properties.

Forced Swim Test

The Forced Swim Test, a widely employed behavioral model for evaluating central nervous system depressant activity in rodents, was performed following the methodology proposed by Porsolt et al. in 1977 [30]. The test procedure closely followed established protocols in the literature.

Rats were individually placed in a transparent glass chamber measuring 25 × 15 × 25 cm filled with fresh water to a height of 15 cm, and the water temperature was maintained at 26 ± 1°C. At this water level, the rats were unable to touch the bottom or the chamber's side walls with their hind paws or tail. After each rat's turn, the water in the chamber was replaced with fresh water. During the initial 2-min phase of the 6-min testing period, each animal exhibited vigorous movement. Subsequently, the duration of immobility was manually recorded over the remaining 4 min.

Rats were considered immobile when they ceased active struggling and remained afloat in the water without any significant motion, except for the minimal movements required to keep their heads above water. After the swimming session, the rats were gently towel-dried and returned to their respective housing conditions.

Locomotor Activity

The independent measurement of spontaneous locomotor activity for each mouse was conducted over duration of 10 min using an actophotometer. Prior to the test, the peel extracts and the polyherbal formulation (PHF) were administered 60 minutes in advance, while the standard drug Imipramine hydrochloride was administered 60 minutes before the test [31].

Muscle Co-ordination Test

The rotarod test was conducted utilizing a specialized rotarod apparatus. This apparatus featured a metal rod with a diameter of 3 cm, coated with rubber, and connected to a motor set to rotate at a speed of 20 rotations per min. The length of the rod was 45 cm, and it was divided into three sections by metallic discs, which enabled the concurrent testing of three rats. The rod was positioned approximately 50 cm above the tabletop to deter the animals from leaping off the roller. Cages positioned beneath the sections were in place to confine the movements of the animals in case they fell from the roller. Prior to the formal test, albino rats

underwent a pre-test on the apparatus. Only those animals that demonstrated their capability to remain on the revolving rod (at 20 rpm) for duration of 5 minutes were selected for the test [32].

RESULT AND DISCUSSION

Preliminary Phytochemical Analysis

The preliminary phytochemical screening of aqueous extracts of the four peels revealed compounds mentioned in Table 1.

Table 1. Preliminary phytochemical analysis of aqueous extracts from selected fruit peels

Phytoconstituents	Tests	<i>A. squamosa</i>	<i>A. deliciosa</i>	<i>C. melo</i>	<i>M. pumila</i>
Alkaloids	Dragendorff's test	+	-	-	-
	Mayer's test	+	-	-	-
Glycosides	Shinoda test for Flavonoids	-	-	-	+
Phenolics	5% FeCl ₃	+	+	+	+
Carbohydrates	Molisch's Test	+	-	+	-
Amino acids	Ninhydrin test	-	-	-	-
Saponins	Foam test	-	-	+	-
Tannins	Gelatin test	+	-	+	-

"+" denotes present, "-" denotes absent

Acute Toxicity

The rats were normal and no toxic signs were seen after administration of the peel extracts. There was no mortality at the highest dose of 2000 mg/kg. Hence, dosages for pharmacological studies were selected as 1/5th and 1/10th of the highest dose (2000 mg/kg).

Neuropharmacological Activity

In this study, the peel extracts significantly reduced immobility time compared to the control group. The effectiveness of the treatments was ranked as follows: PHF > APMP > APCM > APAS > APAD (Table 2 and Figure1).

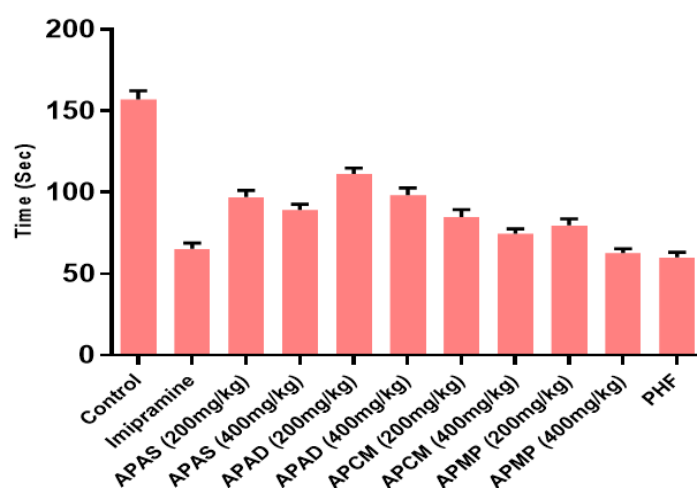


Figure 1. Impact of the chosen peel extracts and polyherbal formulation on immobility duration in the forced swim test

Table 2. Impact of the chosen peel extracts and polyherbal formulation on immobility duration in the forced swim test

Groups	Immobility Time (Sec)						Mean $\pm$ SEM
	R1	R2	R3	R4	R5	R6	
Control	164	172	154	136	150	166	157.00 $\pm$ 5.33
Imipramine	59	66	71	55	62	79	65.33 $\pm$ 3.54
APAS (200 mg/kg)	94	86	106	99	87	111	97.16 $\pm$ 4.12*
APAS (400 mg/kg)	83	76	89	91	94	102	89.16 $\pm$ 3.66*
APAD (200 mg/kg)	123	112	118	108	97	110	111.33 $\pm$ 3.64*
APAD (400 mg/kg)	99	103	87	111	107	82	98.16 $\pm$ 4.66*
APCM (200 mg/kg)	88	69	77	82	99	94	84.83 $\pm$ 4.52*
APCM (400 mg/kg)	64	75	82	68	79	80	74.66 $\pm$ 2.94*
APMP (200 mg/kg)	77	82	65	74	88	92	79.66 $\pm$ 4.00*
APMP (400 mg/kg)	61	72	60	54	59	70	62.66 $\pm$ 2.82*
PHF	66	54	62	71	58	49	60.00 $\pm$ 3.27*

$p < 0.05$ * significance followed by one way ANOVA followed by DUNNETT's multiple comparison test

The rotarod test is employed to assess skeletal muscle relaxant activity. This test is utilized to evaluate the effects of drugs on motor coordination. Dunham and Miya (1957) proposed that the muscle relaxation induced by a test compound could be assessed by measuring the rats' ability to remain on a rotating rod. The selected peel extracts showed a highly significant reduction in the time spent by the animals on the rotating rod when compared to the control ($p < 0.05$). The standard drug (diazepam) also exhibited a highly significant effect when compared to the control (Table 3 and Figure 2). The order of potency was found to be PHF>APCM>APMP>APAD>APAS. The selected extracts displayed dose-dependent effects on muscle coordination, as assessed by the rotarod method. The results from the rotarod test clearly demonstrated the significant muscle relaxation activity induced by the extracts in the tested animals.

Table 3. Impact of the chosen peel extracts and polyherbal mixture on the duration of time spent in the rotarod apparatus

Groups	Time (Sec)						Mean $\pm$ SEM
	R1	R2	R3	R4	R5	R6	
Control	175	152	134	154	143	161	153.16 $\pm$ 5.80
Diazepam(2 mg/kg)	44	56	39	52	61	71	53.83 $\pm$ 4.72
APAS (200 mg/kg)	123	114	116	130	104	106	115.50 $\pm$ 4.04*
APAS (400 mg/kg)	111	99	85	121	101	100	102.83 $\pm$ 4.96*
APAD (200 mg/kg)	102	94	116	111	102	99	104.00 $\pm$ 3.29*
APAD (400 mg/kg)	92	101	87	117	101	94	98.66 $\pm$ 4.27*
APCM (200 mg/kg)	92	89	87	102	92	80	90.33 $\pm$ 2.95*
APCM (400 mg/kg)	62	71	79	80	61	79	72.00 $\pm$ 3.57*
APMP (200 mg/kg)	89	102	111	94	88	102	97.66 $\pm$ 3.63*
APMP (400 mg/kg)	79	84	69	97	84	76	81.50 $\pm$ 3.85*
PHF	38	52	41	50	49	34	44.00 $\pm$ 3.00*

$p < 0.05$ * significance followed by one way ANOVA followed by DUNNETT's multiple comparison test

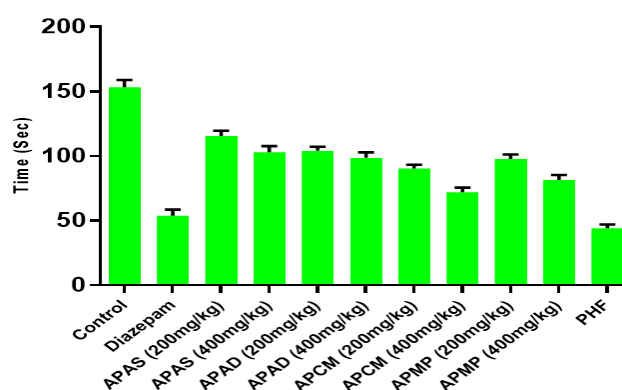


Figure 2. Impact of the chosen peel extracts and polyherbal mixture on the duration of time spent in the rotarod apparatus

Locomotor activity serves as an indicator of alertness, and a decrease in activity is indicative of sedative effects. The decreased mobility observed in the control rats may be attributed to the monoamine theory of depression, leading to depleted monoamines in the brain, consequently resulting in hypothermia and reduced mobility. However, both the standard drug and the selected peel extracts exhibited significant antidepressant activity, as evidenced by increased alertness and heightened mobility across the cell beams. Table 4 and Figure 3 illustrated that the locomotor activity in the treatment groups followed this order: PHF>APMP>APCM>APAD>APAS.

Table 4. Impact of the chosen peel extracts and polyherbal mixture on the locomotor activity in the actophotometer

Groups	Locomotors activity (Sec)						Mean $\pm$ SEM
	R1	R2	R3	R4	R5	R6	
Control	94	77	80	93	89	76	84.83 $\pm$ 3.32
Imipramine	120	103	96	88	109	111	104.50 $\pm$ 4.65
APAS (200 mg/kg)	98	100	110	97	100	90	99.16 $\pm$ 2.63*
APAS (400 mg/kg)	113	104	98	111	92	117	105.83 $\pm$ 3.91*
APAD (200 mg/kg)	99	104	98	96	89	86	95.33 $\pm$ 2.72*
APAD (400 mg/kg)	118	100	104	111	102	99	105.66 $\pm$ 3.01*
APCM (200 mg/kg)	99	101	110	89	104	99	100.00 $\pm$ 2.87*
APCM (400 mg/kg)	120	113	99	104	101	107	107.33 $\pm$ 3.23*
APMP (200 mg/kg)	105	89	102	104	100	90	98.33 $\pm$ 2.88*
APMP (400 mg/kg)	121	111	106	99	127	117	113.50 $\pm$ 4.17*
PHF	131	124	127	104	119s	126	121.83 $\pm$ 3.91*

$p < 0.05$ * significance followed by one way ANOVA followed by DUNNETT's multiple comparison test

Various medications, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective reversible inhibitors of monoamine oxidase A (RIMAs), and specific serotonin–noradrenaline reuptake inhibitors (SNRIs), are commonly prescribed for therapeutic purposes. However, these drugs are associated with a range of side effects, such as cardiac toxicity, hypotension, sexual dysfunction, weight gain, and sleep disturbances.

Depression has a high incidence rate within communities, and it is directly or indirectly linked to morbidity and, to some extent, mortality. In the Forced Swim Test (FST), rats compelled to swim within a confined space eventually cease swimming and become motionless. This behaviour is

referred to as immobility and signifies a state of lowered mood. Agents that diminish this despondent behaviour is classified as antidepressant drugs.

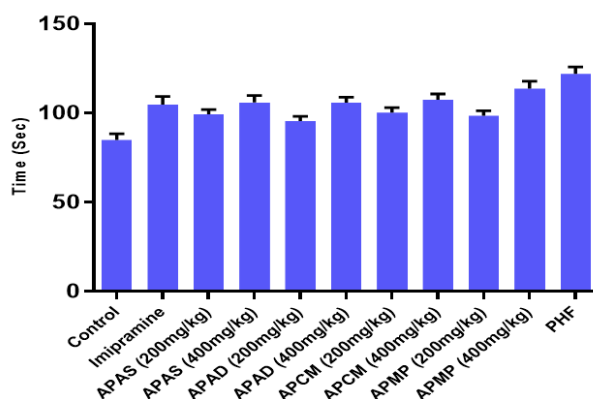


Figure 3. Impact of the chosen peel extracts and polyherbal mixture on the locomotor activity in the actophotometer

The FST serves as a highly sensitive test for assessing alterations in monoamines and represents a specific cluster of stress-induced behaviours not necessarily related to depressive symptoms in humans. Nonetheless, it is remarkably responsive to manipulations of monoaminergic systems. Furthermore, it offers a valuable model for investigating the neurobiological and genetic mechanisms underpinning stress and responses to antidepressants. These screening tests are highly sensitive and widely utilized for the assessment of rodent behaviours to predict antidepressant potential, as indicated by a decrease in immobility time [30].

The Forced Swim Test (FST) results highlighted the capacity of these extracts to reduce immobility time in rats, indicative of their potential antidepressant properties. Notably, the polyherbal mixture (PHF) exhibited the highest potency in this regard, followed by the individual fruit peel extracts. The Rotarod test, which assessed muscle coordination and relaxation, further underscored the potential therapeutic value of these extracts. The selected extracts demonstrated a notable reduction in the time spent by animals on the rotating rod, indicating their ability to induce muscle relaxation. Again, the polyherbal mixture (PHF) exhibited remarkable efficacy in this aspect [30].

Furthermore, the locomotor activity results indicated that the selected peel extracts, as well as PHF, exhibited antidepressant activity by increasing alertness and mobility, which contrasted with the reduced mobility observed in the control group [31,32].

This study sheds light on the neuropharmacological properties of fruit peel extracts from *A. squamosa*, *C. melo*, *A. deliciosa*, and *M. pumila*. The extracts demonstrated significant activity in behavioral models such as the Forced Swim Test, Rotarod Test, and locomotion assessment, suggesting their potential as antidepressant, neuromuscular, and stimulatory agents. These activities can be attributed to the presence of bioactive compounds, including polyphenols and flavonoids, known for their antioxidant and neuroprotective effects.

Notably, there are no prior studies reported in the literature investigating the neuropharmacological activities of these specific fruit peels or the fruits themselves, highlighting the novelty of this research. To strengthen the discussion, future studies should compare these findings with similar investigations on other fruit peels or plant-derived compounds that have demonstrated neuropharmacological potential. This would provide a more comprehensive context for the observed results and facilitate a deeper understanding of their pharmacological mechanisms.

This work emphasizes the need for further exploration of agro-industrial by-products, such as fruit peels, as cost-effective, sustainable sources of therapeutic agents. It also opens avenues for future research focused on standardization of extraction methods, dose optimization, and clinical validations

to establish these extracts as viable candidates for treating neuropsychiatric and neurodegenerative disorders. Such efforts would align with global initiatives to reduce waste while harnessing the untapped potential of natural resources for pharmaceutical innovation.

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AUTHOR CONTRIBUTIONS

Concept: A.K.D., V.S.P., G.M.K.; Design: A.K.D., V.S.P., G.M.K.; Control: A.K.D., V.S.P., G.M.K.; Sources: A.K.D., V.S.P., G.M.K.; Materials: A.K.D., V.S.P., G.M.K.; Data Collection and/or Processing: A.K.D., V.S.P., G.M.K.; Analysis and/or Interpretation: A.K.D., V.S.P., G.M.K.; Literature Review: A.K.D., G.M.K.; Manuscript Writing: A.K.D., V.S.P., G.M.K.; Critical Review: A.K.D., V.S.P., G.M.K.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

All aspects related to the housing, handling, and experimental procedures involving the animals strictly adhered to the regulations set forth by the Institutional Animal Ethics Committee (Registration No. 516/01/A/CPSCEA).

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