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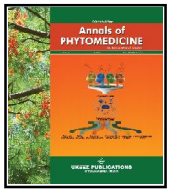

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Isolation, characterization and evaluation of semi-synthetic of hesperidin derivatives from *Citrus aurantium* L.

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Abstract

The plant, *Citrus aurantium* L., also famous as the bitter orange, is a member of the Rutaceae family and is widely available. Citrus fruits are well-known sources of flavonoids, which could be beneficial for health due to their antioxidant, anti-inflammatory, anticancer and antianalgesic properties. The main bioactive components of citrus fruit are flavonoids, especially naringin, hesperidin, alkaloids, synephrine and vitamin C. The peel extract of *C. aurantium* and their semi-synthesized compound were evaluated for analgesic and antioxidant activity using diclofenac and ascorbic acid as standard drug, respectively. Compound hesperidin (HA1) was isolated from methanolic extract of *C. aurantium* peel by using Soxhlet apparatus before isolation orange peel was de-fated by n-hexane, further hesperidin was converted to hesperitin (HA2) by using sulphuric acid and methanol. At last, bromination of compound hesperitin was performed to get novel compound (HA3). The analgesic activity was done *via* eddy is hot plate method and antioxidant activity was performed by DPPH method. All the compounds were evaluated for structural conformation by using IR, 1H-NMR and mass spectra were used to proved the structure of the final analogues. All IR, 1H-NMR, and mass spectra results were found to be well interpreted for the confirmation of HA3 compound. It was found that semi-synthesized compound showed the maximum analgesic activity as 48 ± 0.67 after 1h and as well as antioxidant activity 75.52% at 800 µg/ml concentration on comparison to both the standard drugs.There are many commercial products with hesperidin and its derivatives in both the domestic and global markets.The finding that hesperidin derivatives could be useful as analgesic and antioxidant agent. Further, research on hesperidin for the discovery as a potent analgesic agent is required, to syntheize different derivatives as a good lead molecule with better pharmacological profile.

1. Introduction

Plants and their products have been used as a source of food and medicine since humanity developed. Illness and health have always coexisted. Through experiments, the therapeutic effects of plants would have been discovered. These plants derivatives or their chemical constituents have long history in the field of healing and treatment of disease or clinical use acceptance and better patient tolerance. In India, traditional medicine has been used for many years. Since 4500 BC, many kinds of Ayurveda, Unani, Siddha and have been practised (Warrier *et al*., 2021). Between 35,000 and 70,000 plant species have been investigated for their potential as medicines. *C. aurantium* (orange peels) is the outer part of plant belonging to *Rutaceae* family. Orange peels is the very important citrus fruit in the world. Generally, cultivated in the tropical region (Sottile *et al*., 2019).

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Pain is typically defined as a bad sensation and emotional experience brought on by tissue damage, or as it can be perceived around such damage. International association for the study of pain defines, inflammation is a tissue's immune reaction to any acute or chronic injury as evidenced by an accumulating amount of white blood cells and antibodies, swelling and fluid build-up at the injured site (Ali *et al.*, 2022).

Hesperidin was first isolated from orange peels in 1828. Orange peels contain hesperidin as an bioflavonoid at high concentration. The citrus sector is one of the most important in the agro-industrial system when it comes to processing fruits. Brazil produced 64 per cent of the world's orange juice in 2018/19, with 87 per cent of that being sold internationally. The major biological active constituents in the citrus fruit are flavonoids, particularly naringin, hesperidin, alkaloids, synephrine, tyramine, N-methyltyramine, hordenine and vitamin C. Citrus fruits are well-known sources of flavonoids, which may have health-promoting qualities such as antioxidant, anti-inflammatory, anticancer, antianalgesic signaling and neuroprotective activity. Citrus flavonoids have also been linked to the treatment of vascular disorders, as vasoconstriction, blood pressure and bronchial muscular relaxation. Its fruit extracts have been used to treat a variety of illnesses, including cancer, cardiovascular disease, sleeplessness, headaches and stomach issues.They are also antibacterial,

antispasmodic, aromatic, astringent, carminative, digestive, sedative and stimulant (Bino *et al*., 2018). Hesperidin occurs naturally in citrus fruits in the aglycone form as hesperitin. It is a member of a class of flavonones. It used as anti-inflammatory, antiallergic, hypolipidemic, vasoprotective, antioxidant and anticarcino genic.Taking into account all of these details, the study's objective is to ascertain the analgesic and antioxidant activity of a 6,8-dibromo-5,7-dihydroxy-2-(3-hydroxy-4methoxyphenyl)-4 H-chromen-4-one (HA3) derivatives that has been synthesized as a potent drug for treating pain. It would be an efficient, affordable and complementary therapy that could replace the use of current medications.

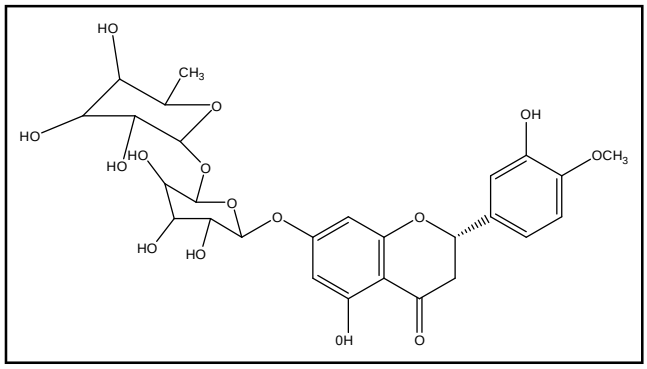

Figure 1: Structure of hesperidin.

2. Materials and Methods

2.1 Chemical and reagents

Methanol, n-hexane, glacial acetic acid, sulfuric acid and silica gel were bought from the Avantor Performance Material India limited and acetone, brominewere bought from the Central Drug House (P). Ltd., New Delhi and distilled water from the own institution.

2.2 Collection of plant material

Peels of *C. aurantium* were collected in the fruit market, Lucknow, U.P., India. This project was approved by HIPER/2021-22/118 and authenticated by NISCPR/RHMD/Consult/ 2022/4002-03.

2.3 Isolation of crude hesperidin

Air-dried orange peel was extracted in Soxhlet assembly with different solvents in a series of solvent extractions like n-hexane, petroleum ether, chloroform, 95% ethanol and water.

2.4 Procedure for isolation and purification hesperidin from *C. aurantium*

100 g powered air dried orange peels was extracted by Soxhlet apparatus for an about 1 h with n-hexane (400 ml) on water bath. The extract was filtered while hot through a buchner funnel and marc is dried at room temperature. Extract the powder under refluxing for 4 h with 400 ml methanol. Filter while hot and wash the marc with 50 ml of hot methanol, add the washing to the filtrate. Concentrate the combined filtrate under the reduced pressure to syrupy mass. The extract was acidified with dil. acetic acid and left for 3 to 4 h and yield crude hesperidin, melting point was 240-240^{o}C (hesperidin was extracted with multiple process due to low yield). The IR, NMR and Rf value of product was found for structural conformation of compounds. The Rf value was found to 0.61 using n-Butanol: water: Acetic acid (3:1:1) (Bharti *et al.,* 2021).

2.5 Procedure for conversion of hesperidin in to hesperitin

Take 9 g powder of hesperidin with methanol (250 ml) and concentrated sulphuric acid (9 ml) and was stirred and reflux for 8 h. The homogenous liquid extract was cooled. Concentrated by evaporation and then diluted with ethyl acetate (500 ml). The organic solution was washed and dried magnesium sulphate after being washed with water. For purification of hesperitin, dissolving the crude product in a few ml of acetone and then adding the standard solution to a vigorously stirred solution of water and acetic acid. Water is used to wash and cool precipitated hesperitin in an ice bath. Hesperitin is purified into a pure yellow powderand melting point was 230-232^{o}C (Lahmer *et al*., 2015).

2.6 Procedure for synthesis of hesperitin derivatives

Take 1.0 g of hesperitin and dissolve it in 12 ml of glacial acetic acid. Carefully continue stirring in 2 ml of liquid bromine to the mixture. Allow the mixture to stand for 15 min or until the bromine colour persists. Add 80 ml of water. At the pump, remove the bromo compound using a filter before washing with a little cold water. Hesperidin derivatives melting point was 140-142 (Furniss *et al*., 2016).

2.7 Analgesic activity

According to the method reported in the literature (Vabeiryureilai, *et al*., 2015), the preliminary test of target compound was completed by using eddy's hot plate technique. This project was approved by International Animal Ethical committee at Hygia Institute of Pharmaceutical Education and Research, Lucknow (Ref. NO. HIPER/IAEC/91/02/2022). The hot plate test is used to test the analgesic activity of substances. The hot plate had a metallic surface (diameter 20 cm, height 2.0 cm) and a temperature of 55. To prevent heat loss, each mouse was placed on the heat hot plate and enclosed with a glass breaker. Note, how long it took you to lick the force paw or jump. The latency period/reaction time for everyone was then recorded thirty minutes following administration. Each group was usually taken up of three mice. In group-I Hesperidin (HA1)100 mg/kg b.wt, group-II Hesperitin (HA2),100 mg/kg b.wt, group-III novel (HA3)100 mg/kg b.wt, group-IV control,100 mg/kg b.wt and group-V standard 20 mg/kg b. wt (Vabeiryureilai *et al*., 2015).

$$\text{The pain inhibition (per cent)} = \frac{\text{Post treatment latency(s)} - \text{Pretreatment latency (s)}}{\text{Pretreatment latency (s)}} \times 100$$

2.8 Antioxidant activity

Antioxidant activity *in vitro* the most outstanding, easiest and widely used approach for assessing preliminary free radical-scavenging activity is the DPPH method. DPPH behaves as a stable and effective free radical with an odd electron in its 1 structure that is commonly used in chemical analysis to determine radical scavenging action. Labile hydrogen is reported to be abstracted by DPPH using the stable radical DPPH, the DPPH-radical scavenging activity of synthesised compounds (HA3) was assessed in terms of radical-scavenging ability. A DPPH solution was produced and applied at various doses (1-1000 mg/ml) to all of the generated compounds (HA3). The absorbance for compounds was recorded at 517 nm thirty minutes later. The UV-visible spectrophotometer was used for all of the analysis. The per cent inhibition was estimated using

the absorbance of various concentrations. The usual antioxidant was ascorbic acid. The IC_{50} value is the sample concentration required to scavenge 50 per cent of the DPPH free radical. The per cent inhibition vs. concentration graph was used to calculate the IC_{50} of all produced compounds (HA3). The compound was showing the maximum antioxidant activity 75.52 per cent at 800 µg concentration on comparison to the standard drugs (Yeligar *et al*., 2021; Kumari *et al*., 2020; Yogi *et al*., 2016).

DPPH radical scavenging activity (per cent)

$$= \frac{AC517 - AE517}{AC517} \times 100$$

where; AC517 is absorbance of a DPPH solution without fraction. AE517 is the absorbance of the tested compounds with DPPH.

Table 1: Comparison between antioxidant activity of standard, isolated compound and its derivatives

Concentration (µg/ml)	200 µg	400 µg	600 µg	800 µg	1000 µg
Percentinhibition hesperidin (HA1)	42.2	50.3	62.9	67.37	78.48
Percentinhibition hesperitin (HA2)	32.38	39.35	45.19	48.41	54.8
Percentinhibition novel compound (HA3)	12.12	53.1	69.5	75.52	87.9
Percent inhibition standard	29.26	54.8	60.22	75.9	100

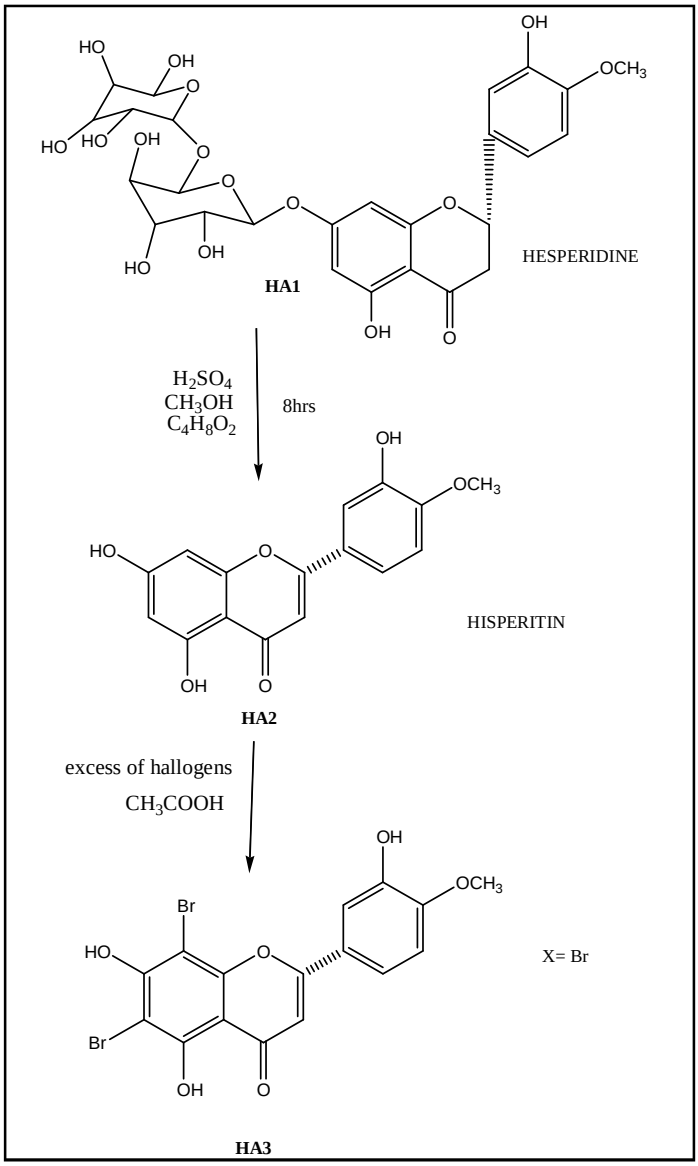

Figure 2: Structure of hesperidin derivative.

2.9 Scheme

Table 2: Physiochemical properties of compounds

S. No	Compound code	Molecular weight	Molecular formula	TLC Rf value	Melting point	Percentage yield	Colour
1	Hesperidin (HA1)	610.6	$C_{28}H_{34}O_{15}$	0.61	240-242	2 per cent	Yellowish
2	Hesperitin (HA2)	302.28	$C_{16}H_{14}0_{16}$	0.63	230-232	38 per cent	Yellowish
3	Novel compound (HA3)	460.07	$C_{16}H_{12}Br_2O_6$	0.71	140-142	25 per cent	Light brown

Hesperidin (HA1) (Lahmer *et al*., 2015)

Light yellow solid, Yield: 2 per cent M.P.: 240-241^{o}C, IR (KBr, t/cm^{-1}) 3546 (C-OH), 2919(C-H, Ar), 1601 (C=C, Ar), 1576 (C=O), 1180 (C-O), 1H NMR (DMSO-d6, 400 MHz) d 12.80 (s, Ali-H, 1H), 8.01 (m, Ar-H, 2H), 7.11 (m, Ar-H, 2H), 6.90-6.82 (s, Ali-H, 4H), 6.40-5.00 (s, Ali-H, 3H), 4.51 (s, Ali-H, 2H), 3.80 (s, Ali-H, 3H), 3.21–3.62 (m, Ar-H, 7H), 3.22–3.61 (m, Ar-H, 5H), 2.50 (m, Ar-H, 2H), 1.12 (m, Ali-H, 3H) EIMS (m/z): 610.37 $[M]^{+}$, 611.09 $[M]^{+1}$.

Hesperitin (HA2) (Lahmer *et al*., 2015)

Light yellow solid, Yield: 38 per cent M.P.: 230-231^{0}C, IR (KBr, t/cm^{-1}) 3650 (C-OH), 2914 (C-H, Ali), 1653 (C=C, Ar), 1472 (C=O), 1107 (C-O),^{1}H-NMR (300, MHz, DMSO-d_6):6.92-6.77 (m, Ar-H, 3H), 6.44 (s, Ali-H, 1H), 5.88 (m, Ar-H, 2H), 5.48-5.01 (m, Ar-OH, 3H), 3.76 (m, Ali-H, 3H), EIMS (m/z): 300.1 $[M]^{+}$, 301.01 $[M]^{+1}$.

6,8-dibromo-5,7- dihydroxy-2-(3-hydroxy-4methoxyphenyl)-4H-chromen-4-one(HA3)

Light brown solid, Yield: 25 per cent M.P.: 140-141^{0}C.

IR (KBr, t/cm^{-1})3616 (C-OH), 3005 (C-H, Ali), 2848 (C-H, Ar), 1653 (C=C, Ar), 1520 (C=O), 1147 (C-O), 761 (C-Br, Ar).

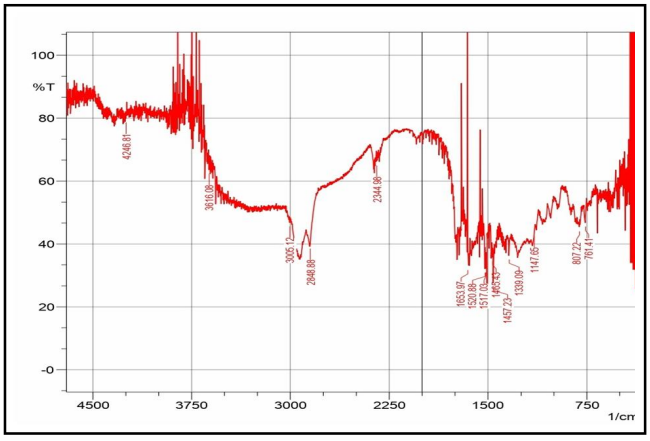

Figure 3: IR spectra of 6,8-dibromo-5,7- dihydroxy-2-(3-hydroxy-4methoxyphenyl)-4H-chromen-4-one (HA3).

H-NMR (300, MHz, DMSO-d_6):6.85-6.55 (m, Ar-H, 3H), 6.14 (s, Ar-H, 1H), 5.8-5.61 (m, Ar-H, 3H), 3.75 (s, Ali-H, 3H).

3. Results

3.1 Preparation of orange peels powder and extracts

Orange peel that was freshly picked, naturally ripened and unpigmented was shade-dried for two to three days before being crushed to create a fine powder. Around 100 g of dried orange crushed powder was produced from 200 g (wet weighted) of orange peel (Figure 4). 100 g of dried orange and previously crushed powder was weighed and extracted with 400 ml of methanol as the solvent. The obtained crude hesperidin extracted from *C. aurantium* was about 2% yield.

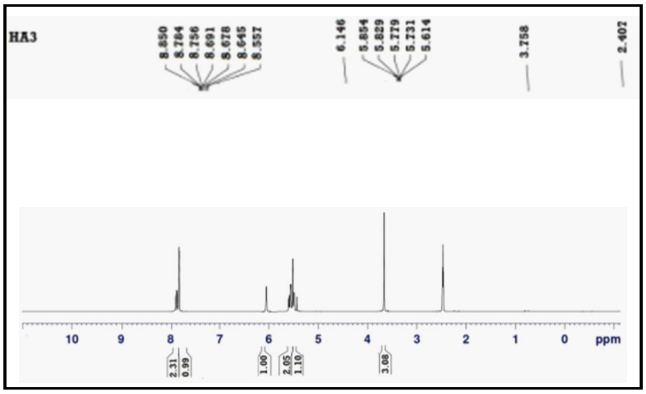

Figure 4: ^{1}H-NMR spectra of 6,8-dibromo-5,7- dihydroxy-2-(3-hydroxy-4methoxyphenyl)-4H-chromen-4-one (HA3).

Figure 5: Dried orange peels powder.

3.2 Analgesic activity

3.2.1 Hot plate method

Table 2 data was obtained by the hot plate method evaluation of analgesic activity. Hesperidin hespeitin and HA3 were administered to mice in various time, resulted in a significant analgesic effect. The

maximum analgesic effect HA3 was seen as 48 ± 0.67 after **that** dose of 100 mg/kg b. wt. Hesperidin, was found to produced maximum pain inhibition activity on comparision to hesperitin but the maximum activity was recorded by compound HA3, among all the three compounds tested for analgesic activity in comparision to standard drug diclofenac.

Table 3: Analgesic activityof hesperidin, hesperitin and novel compound

Compound	Doses (mg/kg)	30 min Mean ± SEM	1 h Mean ± SEM	2 h Mean ± SEM	3 h Mean ± SEM
Hesperidin (HA1)	100	30 ± 0.96*	34 ± 1.19*	38 ± 0.39*	26 ± 0.76
Hesperitin (HA2)	100	21 ± 1.67*	24 ± 1.41*	29 ± 1.38*	18 ± 1.18*
HA3	100	44 ± 1.52**	48 ± 0.67**	52 ± 1.76*	35 ± 1.14*
Control		4 ± 0.28	6 ± 0.62	8 ± 0.46	3 ± 0.56
Standard	20	50 ± 0.74	58 ± 1.67	69 ± 1.27	43 ± 1.21

Data are expressed as Mean reaction time ± SEM. Statistical analysis was performed using two-way ANOVA, followed by Dunnett's $^{***}p<0.001$ vs control; $^{**}p<0.05$ vs control; $^{*}p<0.01$ vs control.

3.3 Antioxidant activity by DPPH radical scavenging activity

The methanolic extract of orange peel and its derivative compound capably scavenged the free radical formed from the DPPH reagent. DPPH method is one of oldest method for antioxidant activity. This method was used for evaluating the antioxidant activity of all the compounds. It was found that compound HA3 has expressed the maximum antioxidant activity and compound hesperidin shows moderate kind of activity against the standard compound vitamin C (ascorbic acid). The graph is mentioned in to the Figure 5.

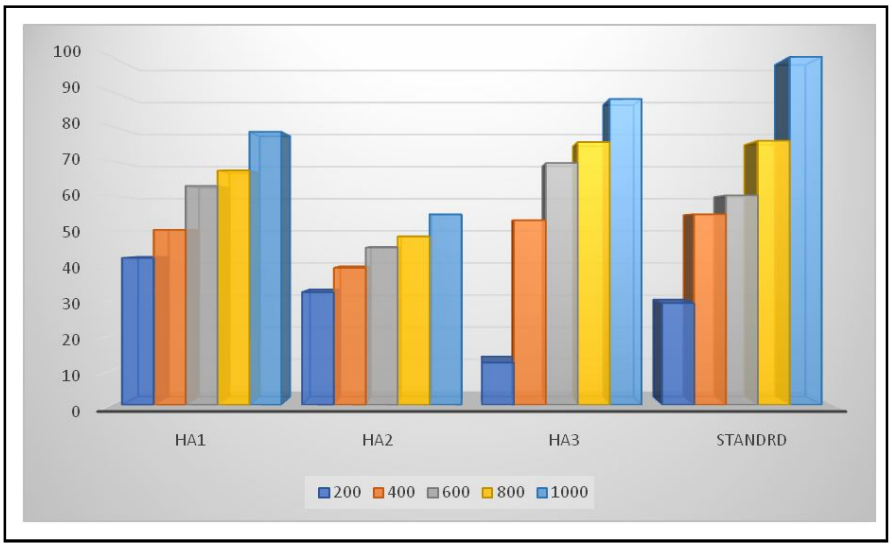

Figure 6: DPHH scavenging assay of synthesized compounds related with standard ascorbic acid (per cent of inhibition vs concentration).

3.4 Ash value

The ash value of orange peel was determined to check the purity of orange peels, the data is calculated by the given formula:

$$\text{Per cent ash} = \frac{w_3 - w_1}{w_2 - w_1} \times 100$$

where, W1 = Weight of empty crucible

W2 = Weight of crucible + Sample before ashing

W3= Weight of crucible + Ash all in grams

Per cent ash was calculated = 2.5 per cent.

4. Discussion

The IR spectra of final 6,8-dibromo-5,7- dihydroxy-2-(3-hydroxy-4methoxyphenyl)-4H-chromen-4-one (HA3) compound shows strong bands in the region 3650 cm^{-1} due to C-OH stretching, 2914 cm^{-1} due to C-H vibration stretching, an intense peak 1653 cm^{-1} is due to C=C aromatic bond, a sharp bond at 761 cm^{-1} was obtained for aromatic C-Br stretching. The ^{1}H-NMR spectrum shows a sharp peek at 6.85-6.55 aromatic hydrogen, a singlet peak at 6.14 was obtained for aromatic hydrogen, a multiple peak was obtained between 5.8-5.61, shows the hydroxyl group present in the compound, a singet peak was obtained at 3.75 shows the presence of methane group.

Orange is a nutritious fruit. The peel of orange considered as typical waste after consumption, which predisposed by orange juice industries. All parts of the orange plant used for its therapeutic property, including the orange peel. Flavonoid, essential oil, phenolics, coumarin, triterpenes, vitamin, carotene, pectin and other compounds play major role in its properties.

Flavonoids are phenolic compounds found in plants that have strong antioxidant properties, the capacity to absorb free radicals and reactive oxygen species and other phenolic compounds. One of the key elements in getting high-quality natural antioxidants is the extraction method. Simple, efficient and environmentally friendly methods should be used. The chosen extraction technique must, however, be extremely effective at removing the most potent chemicals without destroying them. An increase in extraction yield, a decrease in solvent consumption and an improvement in extract quality are just a few advantages of the ideal approach. Peels of *C. aurantium* are a significant source of antioxidant phytocompounds, according to the study (Pandhi *et al*., 2022).Antioxidants can reduce oxidative stress in the body by removing reactive oxygen species from it and protecting or healing the body's damaged tissues.The first line of defence against free radical damage during oxidative stress is provided by antioxidant enzymes like glutathione peroxidase, superoxide dismutase, glutathione reductase and catalase. Non-enzymatic antioxidants like vitamin E (a-tocopherol), vitamin C (ascorbic acid) and glutathione are phenolic compounds that defend by converting oxidants to non-radical end products or moving radicals to locations where their effects are less harmful (Saloni *et al*., 2022).

A common symptom of numerous diseases is pain. It is a crucial objective for healthcare and the primary prognostic indicator for many diseases. Globally, the burden of all types of pain, affecting both adults and children, with or without a known cause, is generally increasing.The most frequent reasons for seeking medical attention are pain and inflammation, which pose a serious healthcare issue. According to the International association for the study of pain, pain is a distressing sensory and emotional involvement that is connected to or resembles the experience of actual or potential tissue damage (Vargas *et al*., 2022). Plants contains a variety of chemicals into their different parts and these chemicals are responsible for different kind of pathological treatments. Hesperidin is the chemical isolated from the orange peels which also gives variety of response to human health. In this research investigation ,we have developed an semi-synthetic compound by hesperidin and evaluated them for analgesic and antioxidant activity. The maximum analgesic activity 48 ± 0.67 after 1h as well as antioxidant activity 75.35 per cent at 800 µg. On evaluation, it was found that compounds show maximum activity in both the test.

5. Conclusion

In the current study, the analgesic and antioxidant activity of crude extracts was assessed. The DPPH free radical scavenging assay was used to assess the crude extracts' capacity to scavenge free radicals.Since the extracts' preliminary phytochemical analysis revealed the presence of phenolic and flavonoid compounds, which are known for their antioxidant properties. Swiss albino mice were used to compare the analgesic effects of hesperidin, hesperitin and semi-synthesized compound (HA3) against diclofenac sodium.The compound hesperidin might to be used as a nutraceutical for preventing inflammation. As such, it may be a potential semi-synthesized derivative for analgesic and antioxidant therapeutics. Further, research on hesperidin moityis needed for discovery as potent analgesic agents. Thus, we observed that there is enough scope for the further research in developing such compounds as good lead molecule with better pharmacological profile.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest relevant to this article.

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