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A Review on Natural Drug Hesperidin

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ABSTRACT :Over the ages, for the food humans are using plants source, cosmetics, medication, clothing and even shelter. In to the health care system plant yields also play a significant role, the remaining 20% of the residents who exist in primarily in advanced countries.India is based on a gold mine of well-documented and conventionally well-practiced expertise in herbal medicine.General phytochemical detection of Citrus sinensis (Orange) belonging to the Rutaceae family exposed the existence of glycoside flavones.The objective of this review is to illustrate the bioactive composite (Hesperidin) from the skin of the fruit C. sinensis.

KEYWORDS: Hesperidin, Flavonoid, Citrus extract, Anticancer, Antiviral

I. INTRODUCTION:

Hesperidin is a chemical substance derived primarily from citrus fruit[1]. It belongs from Biopharmaceutical classification system class-IV (Low Solubility-Low permeability). Plant chemical extract may be used alone or in combination with other plant chemical substances for medicinal purposes. The drug is categorized as flavonoids and may have antimicrobial or antioxidant properties. For that reason, it may affect the human immune system.Along with the effects on the immune system, when combined with other ingredients, hesperidin has proven to have medicinal benefits to the circulatory system of the blood[1-3].

It consists of antioxidants. Hesperidin is known to treat a multiple disease, including lymphedema, haemorrhoids, venous stasis and varicose veins.It is similarlyapplied in therapy of cardiovascular and cerebrovascular diseases as well as in certain cases of abortion[4]. Hesperidin is mainly applied during cancer operations.This means that it may be effective at any stage of cancer therapy.Although toleration of hesperidin supplements is quite high, there are possible side effects.The side effects relate primarily to gastrointestinal reactions.It involves diarrhoea and nausea[5, 6].

Typical hesperidin comes in the usage of dietary supplements such as vitamin C. But they often contain other bioflavonoids. Hesperidin is also presented in other forms such as supplements of the hesperidin complex, combinations with diosmin, different formulations with hesperidin and orange juice with pulp. Because of its forms, hesperidin is often referred to as an over-the-counter drug. Rather, it is regarded as a supplement[5].

A clinical study tested the outcome of the drug on various forms of cancer for example colon cancer, skin cancer, oesophageal cancer and urinary bladder cancer.This research confirmed that hesperidin was stronger than other bioflavonoids and flavonoids. However, further clinical trials are essential to calculate the effects of hesperidin[6].

Hesperidin also has some other names like-Citrus Bioflavonoids, Concentrated Bioflavonoid, Bioflavonoid, Extract Bioflavonoid, Citrus Bioflavones, Complex Bioflavonoid and Extract Bioflavonoid Citrus.

II.DISCOVERY OF HESPERIDIN:

Drug Hesperidin is a glycoside that originates in citrus fruits. The aglycone form of hesperidin is referred to as hesperetin. It is procured from the word "hesperidium", from fruits made by the citrus tree. Hesperidin was earliestsegregated by French chemist LeBreton in1828, from the whitish interior stratum of the citrus peel.Hesperidin is used by plant for defence[7].

III.SOURCE:

Hesperidin is the bestcommunal flavonoid originate in citrus fruits, mainly sweet orange (in

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Immature young oranges constitute nearlyfourteen % of the fresh weight of fruit)[8] and lemon, and accordingly in juices prepared of these citruses. The peel and membrane portions of these fruits acquired the maximum levels of Hesperidin, so hand-pressed juices hold no visible traces of Hesperidin [9]. Commercial juices, meanwhile, are full of withHesperidin for the reason that the industrial fruit processing leads to juices contaminated by peeled components.There are major sources of Hesperidin enlisted in Table No.1

Sr.No.	Source of Hesperidin	Family	Genus	Reference
1.	Citrus unshiu Marcovitc+ C. nobilis Loureiro	Rutaceae	Citrus	[10]
2.	Citrus aurantum	Rutaceae	Citrus	[11]
3.	zanthoxylum gilletii	Rutaceae	Zanthoxylum	[12]
4.	Citrus limon	Rutaceae	Citrus	[13, 14]
5.	Lime	Rutaceae	Citrus	[15]
6.	Agathosma serratifolia	Rutaceae	Agathosma	[16]
7.	Peppermint	Lamiaceae	Mint	[17]
8.	Petitgrain	Rutaceae	Citrus	[18]

Table No:1 Sources of Hesperidin

VI. CHEMISTRY, SOLUBILITY AND PROPERTIES:

Hesperidin (Figure 1) is a flavanone glycoside prepared of aglycone, hespertin or eriodictyol methylic and a disaccharide, rutinose. [19].

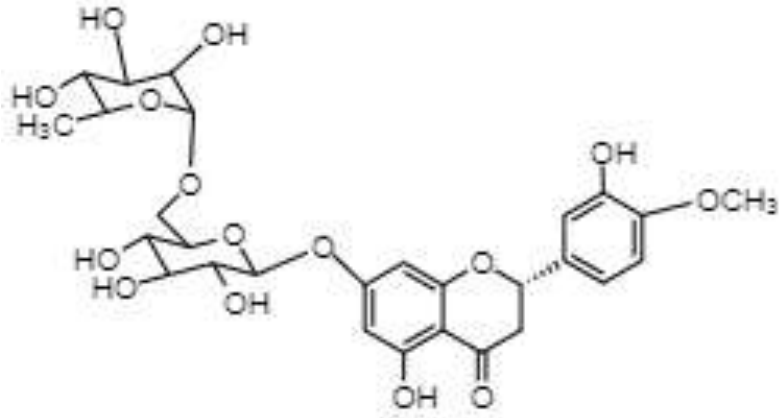

Fig:1. Structure of Hesperidin

Pure hesperidin occurs as long, beige or light-yellow needles. It melts at melting point between the rangeminimum 258° to highest 262°C (make softer at 250°C). Its molecular formula is $C_{18}H_{34}O_{15}$ with a MW of 610.57 Daltons. It is simplyget soluble in to the dilute bases and in pyridine makesanunblemished yellow solution, somewhatmiscible with methanol, warm glacial acetic acid and practically insoluble in acetone,benzene as well as in chloroform. It shows the solubility in water 1 in 50[20]. It has a complex crystal formation nature with other similar glucosides, which significantly disturbs its solubility and other physical properties, makes it challenging to obtain in untainted form[21]. However, it may be refined by washing with warm water and extracting 95% of methyl alcohol, monitored by crystallization[22]. It is distasteful and odourless [23].

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Sr.No	Property	Observation
1	Colour	Light-yellow
2	Odour	Tasteless
3	Test	Odourless
4	Solubility	Solubility in water is 1 in 50
5	Shape of Crystals	Light-yellow needle shape

Table:2 Properties of Hesperidin

Solubility Hesperidin is less soluble in water. The solubility study shows the Hesperidin having a more solubility in the PEG-400 accordingly shown in fig:2[24].

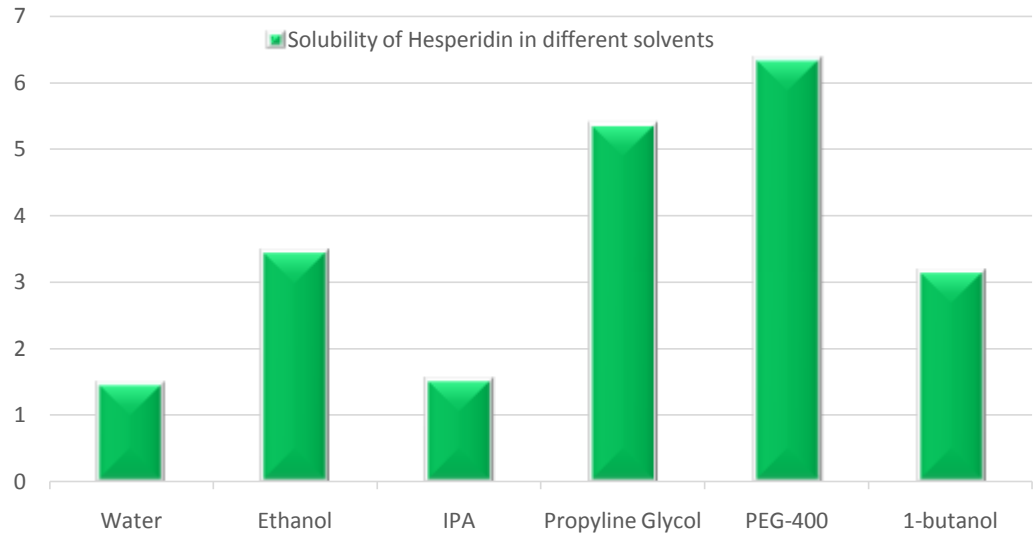

Fig:2 Comparative solubility of Hesperidin in different solvents

V. ISOLATION OF HESPERIDIN:

1.Conventional maceration extraction

In this method the peels of citrus fruit were dipped in aq. ethanol and for extraction kept overnight with agitation at RT (20^0c) [25].

2.Closed-system microwave-assisted extraction

Microwave assisted extraction (MAE) in a closed system was performed with a MicroSYNTH Labstation. A define amount of C. unshiu powder of peel was mixedwith 70% ethyl alcohol andmixed for 5 min, with the microwave-irradiation at60 to180^0 C for 2 to12 min in a closed-vessels. The radiation period includes 2 minutes of heating to attain the wanted temperature.Following the MAE, the liqueurs extracted and keep for cooling at room temperature in an ice bath after filter instantaneously.[25].

3.By using Petroleum ether

Air-dried fresh orange skins were ground to powder and then extracted in sequence, 12 cycles of this triturate were retained in a reflux condenser.Petroleum ether was further added and refluxed for 1.5 h. After filtering the warm combination into a Buchner funnel, the powder was left to dry at room temperature. The dried powder was released back into the flask and methanol was added. Contents were heated by reflux for 2 hours and then filtered hot. With the distillation columnthe filtrate was concentrated, leaving a residue of crystallized syrup made of dilute acetic acid (6%) and giving orange needles[26].

4.Ultrasonic Extraction

The beached powders of 1 g were first added into the 600 ml beaker wrapped by plastic film to circumvent solvent loss and then the extraction solvent was taken with a 1:40 solid-liquid ratio.The trial beakers were submerged in the ultrasound cleaning bath for irradiation.Lastly, the extracts were clarified with a microporous sheath of 0.45 µm and the filtrate was collected. [27].

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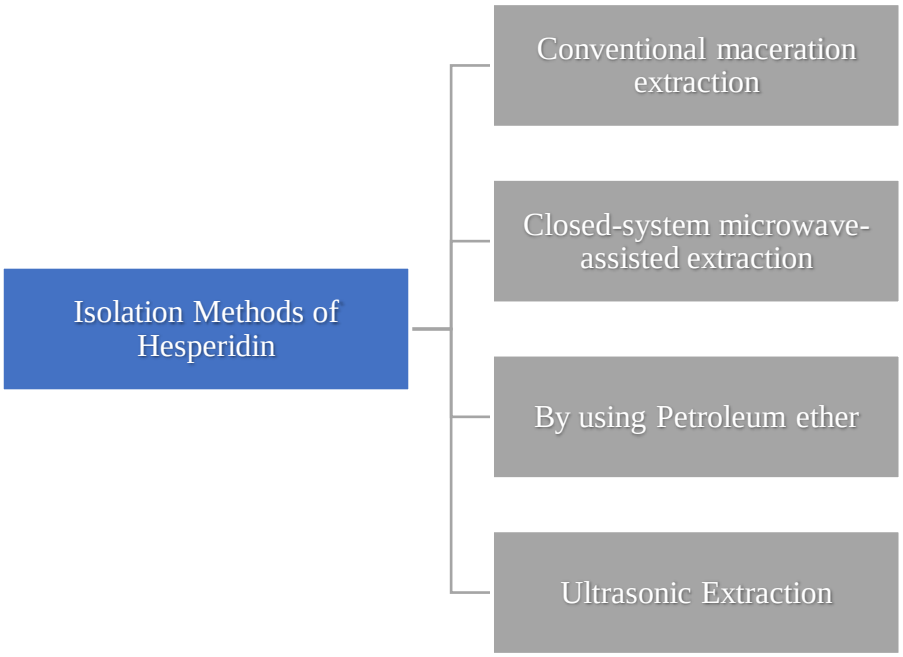

Fig:2 Methods of Hesperidin Isolation

VI.APPLICATIONS OF HESPERIDIN:

There are the following applicationsshown by the hesperidin in following diseases.

1. Neural Diseases:

The many research study displays that hesperidin isoperative and promising action against the neuronal diseases, in that Antidepressant[28],Parkinson[29],Behavioural alterations,[30], Neuroprotective[31],Alzheimer Disease[32].

2 Antiviral Application of Hesperidin:

The precise antiviral action of hesperidin and hesperidin aglycone has been known for an extensive time, grounded on in vitro studies, in particular on the influenza virus and some herpes viruses. [33].Hesperetin inhibition has been accredited to the duplication of the same herpes viruses.Hesperidin also demonstrated a strong constraintresult on rotavirus infectivity, equally in isolation and in essential extracts. In vermin experiments, hesperidin at hundred mg per kg body weight with orally administration,it was establishing to successfullyobstruct the reproduction and spread of influenza A virus by regulating certain autonomous immune responses in cells. [34].

3 Antitumor:

The ability of hesperidin to inhibit tumour growth was evaluated and the use into the various types of cancers. It shows the activity against tumour formation in the study[35].It inhibited the promotion of visible skin tumours more than 2 µm in diameter throughout the period from the 12th to the 20th week[35].

4 Anticancer Activity:

4.1 Gastric cancer:

Apoptic fluctuations such as chromatin condensation, apoptotic morphology of cellular bodiesdeals with SNU-668 Human gastric cells with hesperidin demonstrated, modulation of Bcl-2and initiation of Caspase 3, which advisedprobable use of hesperidin in patients with gastric cancer[36].

4.2 Colon cancer:

Ismai et al. (2012) elucidated the obligation of p53 in hesperidin-mediated apoptosis in colorectal cancer cells.The anti-apoptotic outcome of hesperidin was evaluated in expression cells p53 (HCT116 p53+/+) and p53 Knockout (HCT116 p53/). The results displayed that Hsdmeaningfullyintroverted growth and induced the G1 cell cycle in the p53 positive cells relative to the p53 negative cell[37, 38].

4.3 Breast cancer:

Assessment of the apoptotic action of hesperidin in the human breast carcinoma cell lineage (Michigan cancer foundation-7 MCF-7)revealed that hesperidin (80 M) expressivelyinitiated cell shrinkage, vacuolisation,

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plasma membrane blebs, and cell detachment.The anticancer influence was also reported by other apoptotic features such as increased concentration of LDH (lactate dehydrogenase), GSH (glutathione) depletion, DNA destruction, p53 protein build-up and caspase protein stimulation[39].

4.4 Lung cancer:

Lee et al. (2012) showed a hesperidin-mediated new molecular target for apoptosis in MSTO-211H cells, which has been applied as a model for malignant pleural mesothelioma, auncommon kind of cancer that distresses the lung pleura. [40, 41].

4.5 Liver cancer:

While the initiation of apoptosis through caspase has been detected as the classic experience in cancer cell death,caspase independent non-popappliances such as autophagy, mitotic catastrophe, paraptosis etc., may also cure automated cell death in cancerous cells. Paraptosis, a separate mode of cell death, is caused by hesperidin in HepG2 cells. Because the protein kinase ERK1/2, which occurs in paraptosis, is prompted by hesperidin in HepG2 cells, It may perhaps assumed that hesperidin may act as a promising therapeutic agent for liver cancer by causing the death of non-pop-totic cells[42].

5. Ulcer protective potential of hesperidin:

In the research the findings highlight the potential defensiveinfluence of hesperidin in contradiction of indomethacin and HRS, which is concomitant with the capacity to recover free radicals and anti-oxidants in the mucous tissue of the stomach.The antioxidant potential played an central role in avoiding ulcers, as the protection against the ulcer was greaterin contrast to indomethacin, which gives ulceration mainly due to local oxidative destruction[43].

6. Cardiac Disease:

Hesperidin shows the cardioprotectiveeffect in a study with the SLN.The formulation of Hesperidin within SLN significantly improves the solubility, apparent permeability, stability and bioavailability of hesperidin.On treatment with Hesperidin-SLNs effectively mitigates DOX-induced cardiotoxicity by removing oxidative stress and apoptosis[44].Supplementation for 6 weeks with hesperidin may also increase TAC and decrease blood pressure and inflammatory indicators in patients with type 2 diabetes[45].

7.Anti-inflammatory:

Most studies have made it clear that hesperidin is capable of expressively reducing inflammatory intermediaries such as cytokines, enzymes and linkage molecules. The antioxidant effects of hesperidinwere improved by the molecular origin of its anti-inflammatory effects involves altered cellular signalling pathways such as AP-1 and HIF-1α, but exclusively theNFκβ pathway. Thus, numerous studies informedthat these corridors can be modified by hesperidinthrough deterring the phosphorylation of IκB, p38,JNK and ERK in a dose-reliant mode[45-48].

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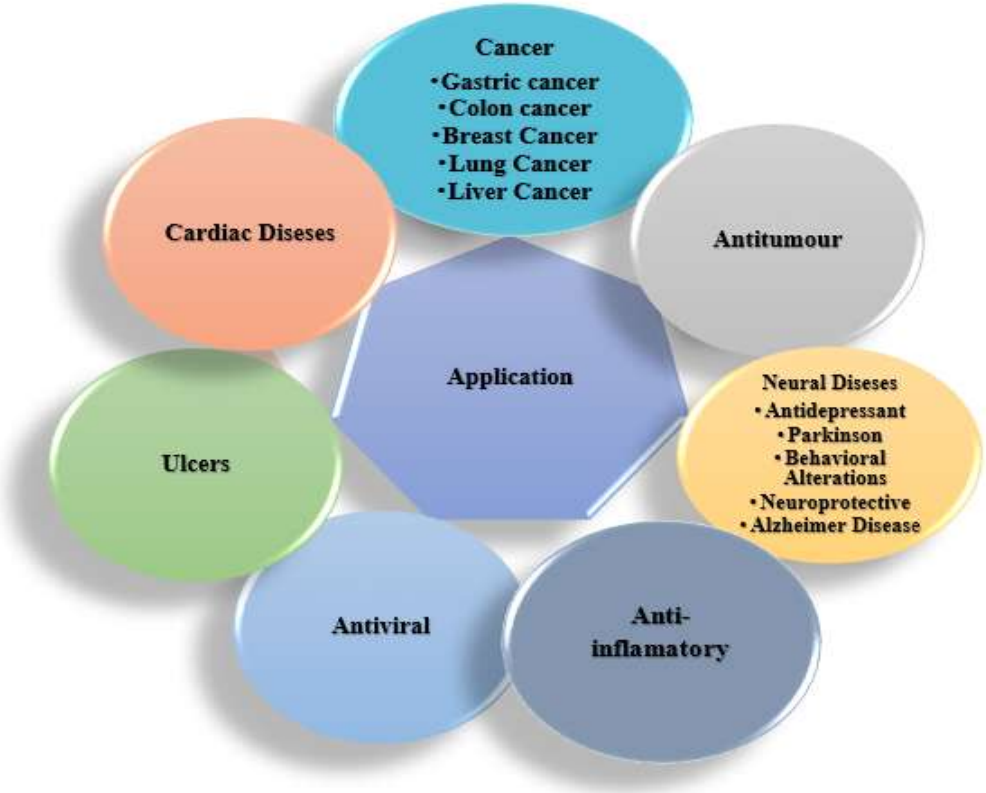

Fig:3 Applications of Hesperidin

VII.DOSAGE FORMS:

1.Cream:

Danijela et.al 2020 Hesperidin is anidentified supplement since of its antioxidant, chelator and anti-aging assets.The application of hesperidin to excludeblack circles, which are delicate and reedy areas of the skin, has been deliberated here. Furthermore, the most operative methods for the nanonisation of hesperidin were discovered, afterwards the nano emulsions were merged into the formulation of cream that was framed for a humid climate.The formulations of silky cream (O/W) were verified in vitro on simulated 3D skin from cultivated cells take out from skin depositslater plastic surgery.One of the nanosized hesperidin formulations has been shown to be the most skin-friendly and can be applied in to the cosmetics.It has been established that nanonised hesperidin preparation is the most skin-approachable and can be applied as a cosmetics[49].

2.Nanoparticles:

Suma Saad et.al.2019prepared solid lipid nanoparticles (SLN) containing Hesperidin by means of supercritical antisolvent (SAS) method to expand oral administration of Hesperidin. Methodfactors were optimised to prepare small (175.3 3.6 nm) SLN-HES with great encapsulation efficiency (87.6 3.8%).Compared to Hesperidin,SLN-HES occasioned in an almost twenty fold rise in aqueous solubility and an almost five fold increase in obvious permeability[44].

Saja H. Ali et. al.2018to increase the constancy and bioactive potentials, hesperidin - PLGA-Poloxamer-407 was effectively prepared to reduce or eliminate the problems related with hesperidin absorption[50].

3.Solid Dispersion:

Polyvinylpyrrolidone (PVP) and Poly-ethylene glycol (PEG) solid dispersal systems with flavanone, naringine and hesperidin glycosides, and their aglycones, naringenine and hesperetin, have been primed, using a SEM (solvent evaporation method), to improve their dissolving proportions that may disturb their bioavailability.The release ability of the both flavanone glycosides and their aglycones was openly influenced by the physical status of solid dispersions[51].

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4. Gastro-resistant Microparticles:

Gastro-resistant microparticles for oral delivery of hesperidin were formed by spray drying with cellulose acetate phthalate (CAP) as an enteric polymer in various polymer/Hesperidinbulk ratios, and a series of dissolution-rate activators, such as cross-linked sodium carboxymethylcellulose (CMC), sodium dodecylbenzene sulphonate (SDBS), or Tween85.The spray drying method and selected process situations were active to microencapsulate and stabilize the flavonoid, resulting in suitable encapsulation ability, productquantity, and micro particles morphology, and a whole drug dissolution in the intestine[52].

5.Nano suspension:

Hesperidin nanocrystals were created from high-pressure homogenization.The overload solubility of spray-dried hesperidin nanocrystals in water be situated 87.2 µg/ml and superior to the hesperidin feedstock. Hesperidin nanocrystals were fully dissolved in fifteen minutes in different solvents. Spray-dried hesperidin nanocrystals improved saturation solubility and particularly the rate of dissolution relative to the raw material, i.e. improved drug administration in the event that the dissolution rate is the rate restrictive step[53].

6. Liposomes:

Modified liposome formulations with a surface loaded with hesperidin have been synthesised with unpredictable amounts of lipids to optimize physico-chemical features. The finest liposomic preparation was then combined with a ligand homing, recognised by HSCs, to obtain a transporter system that assists the aiming of hesperidin. Successful administration was obtained by capturing hesperidin in surface-modified liposomes and pairing them with HSCs-recognized site fixed ligands (M6P BSA)[54].

7. Microbeads:

Marta Tsirigotis-Maniecka et. al. 2014 develop and characterize polyelectrolyte-coated alginate microparticles covering hesperidin a natural bioflavonoid of high nutritiveprospective. The solubility of hesperidin is moderate, so it was critical to prepare a steady carrier that allows its targeted administration to the intestine. The payload was trapped in the alginate hydrogel matrix (ALG) using the external extrusion/frost technique[55].

8.Phospholipid:

The phospholipid complex of hesperidin flavonoid is formulated to improve its dissolution prominent to increased oral bioavailability and the complex was organized by the reflux of several molar ratios of hesperidin and PCs monitored by solvent evaporation. The organized complexes were calculated for saturation solubility, sharing coefficient and drug concentration.The phospholipid complex of hesperidin has antioxidant property and may be used to enhance the dissolution of hesperidin and thus oral bioavailability[56].

9.Transdermal Patch:

Mrinalini C. Damle et. al.2019transdermal patch of drug Hesperidin were synthesised with HPMC E 5, Eudragit S 100 as polymer, dibutyl phthalate as plasticiser and glycerine as emollient.[57].

VIII. MARKETED FORMULATIONS:

Name of Product	Manufacturer	Uses	Reference
Daflon 500mg Tablet	Serdia Pharmaceuticals India Pvt Ltd	-Varicoseveins -Piles -Lymphedema	https://www.zaubacorp.com/company/SERDIA-PHARMACEUTICALS-INDIA-PRIVATE-LIMITED/U52310MH1985PTC037001
Aldosmin 500mg Tablet	Sun Pharmaceutical Industries Ltd	-Varicose veins	https://www.sunpharma.com/
Venostor 500 Tablet	Taj Pharma India Ltd	-Varicose veins	https://www.tajpharma.com/
Presilux Cream	Cadila Healthcare	-Vitiligo -Psoriasis	https://zyduscadila.com/

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	Limited	-self-treatment from the sun's therapeutic UV rays	

Table:2 Marketed Formulations of Hesperidin

IX.TOXICITY PROFILE OF HESPERIDIN:

Acute toxicity study

In the study the vehicle or hesperidin in quantity 55, 175, 550, and 1750 mg/kggiven to theequally male and female rats did not show any marks of inebriation, and entire animals lived through the observation period of fourteen days. Conversely, dosing of hesperidin (5000 mg/kg) revealed a death rate of 10% on day 11 of the post-administration regaining period, relative to the vehicle control set.The acute toxicity data gained using the Karber method specified that the computed median fataldosage (LD50) for hesperidin was 4837.5 mg/kg[58].

X.CONCLUSION:

In the future, phytochemicals may be preferred as hopeful therapeutic agents for neurodegenerative disorders due to their anti-inflammatory and antioxidant activities along with anti-cholinesterase. Neurodegenerative conditions like AD, PD, Huntington, and others share similar characteristics at cellular and sub-cellular levels and sharing mostly joint molecular signalling pathways that can be directed to apoptosis, necrosis and inflammation. Overall, phytochemicals offer capable alternatives to existing therapies for neurodegenerative conditions.

REFERENCES:

[1]. Nardarajah D. Hesperidin-A short Review. Research Journal of Pharmacy and Technology. 2014;7(1):78-80.
[2]. Westerink B, Cremers T. Handbook of Microdialysis–Methods, Applications and Perspectives, Vol. 16: Handbook of Behavioral Neuroscience. Elsevier–Academic Press, Amsterdam, The Netherlands.[Google Scholar]; 2007.
[3]. Rizza S, Muniyappa R, Iantorno M, Kim J-a, Chen H, Pullikotil P, et al. Citrus polyphenol hesperidin stimulates production of nitric oxide in endothelial cells while improving endothelial function and reducing inflammatory markers in patients with metabolic syndrome. The Journal of Clinical Endocrinology & Metabolism. 2011;96(5):E782-E92.
[4]. Kar A. Pharmacognosy and pharmacobiotechnology: New Age International; 2003.
[5]. Milenkovic D, Deval C, Dubray C, Mazur A, Morand C. Hesperidin displays relevant role in the nutrigenomic effect of orange juice on blood leukocytes in human volunteers: a randomized controlled cross-over study. PLoS One. 2011;6(11):e26669.
[6]. Lee N-K, Choi S-H, Park S-H, Park E-K, Kim D-H. Antiallergic activity of hesperidin is activated by intestinal microflora. Pharmacology. 2004;71(4):174-80.
[7]. Lebreton M. Sur la matiere cristalline des orangettes, et analyse de ces fruits non encore developpes, famille des. Hesperidees journal de Pharmacie et de sciences accessories. 1828;14:377.
[8]. Barthe GA, Jourdan PS, McIntosh CA, Mansell RL. Radioimmunoassay for the quantitative determination of hesperidin and analysis of its distribution in Citrus sinensis. Phytochemistry. 1988;27(1):249-54.
[9]. Leuzzi U, Caristi C, Panzera V, Licandro G. Flavonoids in pigmented orange juice and second-pressure extracts. Journal of agricultural and food chemistry. 2000;48(11):5501-6.
[10]. Kurita O, Fujiwara T, Yamazaki E. Characterization of the pectin extracted from citrus peel in the presence of citric acid. Carbohydr Polym. 2008;74(3):725-30.
[11]. Hamdan DI, Mahmoud MF, Wink M, El-Shazly AM. Effect of hesperidin and neohesperidin from bittersweet orange (Citrus aurantium var. bigaradia) peel on indomethacin-induced peptic ulcers in rats. Environmental Toxicology and Pharmacology. 2014;37(3):907-15.
[12]. CYPRIAN HG. EVALUATION OF BIOLOGICAL ACTIVITY OF ALKALOIDS AND FLAVANOIDS IN ZANTHOXYLUM GILLETII (DE WILD

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WATERMAN) EXTRACTS FROM DIFFERENT GEOGRAPHICAL REGIONS IN KENYA: SCHOOL OF PURE AND APPLIED SCIENCES, KENYATTA UNIVERSITY; 2011.

[13]. Papoutsis K, Pristijono P, Golding JB, Stathopoulos CE, Bowyer MC, Scarlett CJ, et al. Screening the effect of four ultrasound-assisted extraction parameters on hesperidin and phenolic acid content of aqueous citrus pomace extracts. Food bioscience. 2018;21:20-6.

[14]. Del Rıo J, Fuster M, Gómez P, Porras I, Garcıa-Lidón A, Ortuño A. Citrus limon: a source of flavonoids of pharmaceutical interest. Food Chem. 2004;84(3):457-61.

[15]. Saeidi I, Hadjmohammadi MR, Peyrovi M, Iranshahi M, Barfi B, Babaei AB, et al. HPLC determination of hesperidin, diosmin and eriocitrin in Iranian lime juice using polyamide as an adsorbent for solid phase extraction. Journal of pharmaceutical and biomedical analysis. 2011;56(2):419-22.

[16]. Ganeshpurkar A, Saluja A. The pharmacological potential of hesperidin. Indian Journal of Biochemistry and Biophysics (IJBB). 2019;56(4):287-300.

[17]. Sroka Z, Fecka I, Cisowski W. Antiradical and anti-H2O2 properties of polyphenolic compounds from an aqueous peppermint extract. Zeitschrift für Naturforschung C. 2005;60(11-12):826-32.

[18]. Suryawanshi JAS. An overview of Citrus aurantium used in treatment of various diseases. African Journal of Plant Science. 2011;5(7):390-5.

[19]. Evans WC. Trease and evans' pharmacognosy E-book: Elsevier Health Sciences; 2009.

[20]. Calomme M, Pieters L, Vlietinck A, Berghe DV. Inhibition of bacterial mutagenesis by Citrus flavonoids. Planta Med. 1996;62(03):222-6.

[21]. Higby RH. Chemical nature of hesperidin and its use as source of vitamin P. J Am Pharm Assoc. 1941;30:629-35.

[22]. King FE, Robertson A. CCXXVIII.—Natural glucosides. Part III. The position of the biose residue in hesperidin. Journal of the Chemical Society (Resumed). 1931:1704-9.

[23]. Kometani T, Nishimura T, Nakae T, Takii H, Okada S. Synthesis of neohesperidin glycosides and naringin glycosides by cyclodextrin glucano-transferase from an Alkalophilic Bacillus Species. Bioscience, biotechnology, and biochemistry. 1996;60(4):645-9.

[24]. Anwer MK, Al-Shdefat R, Jamil S, Alam P, Abdel-Kader MS, Shakeel F. Solubility of bioactive compound hesperidin in six pure solvents at (298.15 to 333.15) K. J Chem Eng Data. 2014;59(6):2065-9.

[25]. Inoue T, Tsubaki S, Ogawa K, Onishi K, Azuma J-i. Isolation of hesperidin from peels of thinned Citrus unshiu fruits by microwave-assisted extraction. Food Chem. 2010;123(2):542-7.

[26]. Lahmer N, Belboukhari N, Cheriti A, Sekkoum K. Hesperidin and hesperitin preparation and purification from Citrus sinensis peels. Der Pharma Chemica. 2015;7(2):1-4.

[27]. Ma Y-Q, Ye X-Q, Fang Z-X, Chen J-C, Xu G-H, Liu D-H. Phenolic compounds and antioxidant activity of extracts from ultrasonic treatment of Satsuma mandarin (Citrus unshiu Marc.) peels. Journal of Agricultural and Food Chemistry. 2008;56(14):5682-90.

[28]. Souza LC, de Gomes MG, Goes AT, Del Fabbro L, Carlos Filho B, Boeira SP, et al. Evidence for the involvement of the serotonergic 5-HT1A receptors in the antidepressant-like effect caused by hesperidin in mice. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2013;40:103-9.

[29]. Kesh S, Kannan RR, Sivaji K, Balakrishnan A. Hesperidin downregulates kinases lrrk2 and gsk3β in a 6-OHDA induced Parkinson's disease model. Neurosci Lett. 2021;740:135426.

[30]. Antunes MS, Ladd FVL, Ladd AABL, Moreira AL, Boeira SP, Souza LC. Hesperidin protects against behavioral alterations and loss of dopaminergic neurons in 6-OHDA-lesioned mice: the role of mitochondrial dysfunction and apoptosis. Metab Brain Dis. 2021;36(1):153-67.

[31]. Cho J. Antioxidant and neuroprotective effects of hesperidin and its aglycone hesperetin. Archives of pharmacal research. 2006;29(8):699-706.

[32]. Thenmozhi AJ, Raja TRW, Janakiraman U, Manivasagam T. Neuroprotective effect of hesperidin on aluminium chloride induced

Alzheimer's disease in Wistar rats. Neurochem Res. 2015;40(4):767-76.
[33]. Garg A, Garg S, Zaneveld L, Singla A. Chemistry and pharmacology of the citrus bioflavonoid hesperidin. Phytother Res. 2001;15(8):655-69.
[34]. Dong W, Wei X, Zhang F, Hao J, Huang F, Zhang C, et al. A dual character of flavonoids in influenza A virus replication and spread through modulating cell-autonomous immunity by MAPK signaling pathways. Sci Rep. 2014;4(1):1-12.
[35]. Berkarda B, Koyuncu H, Soybir G, Baykut F. Inhibitory effect of hesperidin on tumour initiation and promotion in mouse skin. Res Exp Med (Berl). 1998;198(2):93-9.
[36]. Park H-J, Ra J-H, Han M-Y, Chung J-H. Hesperidin induces apoptosis in SNU-668, human gastric cancer cells. Molecular & Cellular Toxicology. 2007;3(1):31-5.
[37]. Ismail IA, Gabry MS, Abdalla SK, Ibrahim MA. P53 SENSITIZES HUMAN COLON CANCER CELLS TO HESPERIDIN THROUGH UPREGULATION OF BAX AND P21. Egyptian Journal of Biochemistry & Molecular Biology. 2012;30(2).
[38]. Saiprasad G, Chitra P, Manikandan R, Sudhandiran G. Hesperidin induces apoptosis and triggers autophagic markers through inhibition of Aurora-A mediated phosphoinositide-3-kinase/Akt/mammalian target of rapamycin and glycogen synthase kinase-3 beta signalling cascades in experimental colon carcinogenesis. Eur J Cancer. 2014;50(14):2489-507.
[39]. Natarajan N, Thamaraiselvan R, Lingaiah H, Srinivasan P, Periyasamy BM. Effect of flavonone hesperidin on the apoptosis of human mammary carcinoma cell line MCF-7. Biomedicine & Preventive Nutrition. 2011;1(3):207-15.
[40]. Lee K-A, Lee S-H, Lee Y-J, Baeg SM, Shim J-H. Hesperidin induces apoptosis by inhibiting Sp1 and its regulatory protein in MSTO-211H cells. Biomol Ther (Seoul). 2012;20(3):273.
[41]. Hsu T-I, Wang M, Chen S, Yeh Y, Su W, Chang W, et al. Sp1 expression regulates lung tumor progression. Oncogene. 2012;31(35):3973-88.
[42]. Yumnam S, Park HS, Kim MK, Nagappan A, Hong GE, Lee HJ, et al. Hesperidin induces paraptosis like cell death in hepatoblatoma, HepG2 cells: Involvement of ERK1/2 MAPK. PLoS One. 2014;9(6):e101321.
[43]. Bigoniya P, Singh K. Ulcer protective potential of standardized hesperidin, a citrus flavonoid isolated from Citrus sinensis. Revista Brasileira de Farmacognosia. 2014;24(3):330-40.
[44]. Saad S, Ahmad I, Kawish SM, Khan UA, Ahmad FJ, Ali A, et al. Improved cardioprotective effects of hesperidin solid lipid nanoparticles prepared by supercritical antisolvent technology. Colloids Surf B Biointerfaces. 2020;187:110628.
[45]. Homayouni F, Haidari F, Hedayati M, Zakerkish M, Ahmadi K. Blood pressure lowering and anti-inflammatory effects of hesperidin in type 2 diabetes; a randomized double-blind controlled clinical trial. Phytother Res. 2018;32(6):1073-9.
[46]. Tejada S, Pinya S, Martorell M, Capó X, Tur JA, Pons A, et al. Potential anti-inflammatory effects of hesperidin from the genus citrus. Curr Med Chem. 2018;25(37):4929-45.
[47]. Guazelli CF, Fattori V, Ferraz CR, Borghi SM, Casagrande R, Baracat MM, et al. Antioxidant and anti-inflammatory effects of hesperidin methyl chalcone in experimental ulcerative colitis. Chemico-Biological Interactions. 2020;333:109315.
[48]. Kuo PJ, Fu E, Lin CY, Ku CT, Chiang CY, Fu MM, et al. Ameliorative effect of hesperidin on ligation-induced periodontitis in rats. J Periodontol. 2019;90(3):271-80.
[49]. Stanisic D, Liu LH, Dos Santos RV, Costa AF, Durán N, Tasic L. New Sustainable Process for Hesperidin Isolation and Anti-Ageing Effects of Hesperidin Nanocrystals. Molecules. 2020;25(19):4534.
[50]. Ali SH, Sulaiman GM, Al-Halbosiy MM, Jabir MS, Hameed AH. Fabrication of hesperidin nanoparticles loaded by poly lactic co-Glycolic acid for improved therapeutic efficiency and cytotoxicity. Artificial cells, nanomedicine, and biotechnology. 2019;47(1):378-94.
[51]. Kanaze F, Kokkalou E, Niopas I, Georgarakis M, Stergiou A, Bikiaris D. Dissolution enhancement of flavonoids by solid dispersion in PVP and PEG matrixes: A comparative study. J Appl Polym Sci. 2006;102(1):460-71.
[52]. Sansone F, Rossi A, Del Gaudio P, De Simone F, Aquino RP, Lauro MR.

Hesperidin gastroresistant microparticles by spray-drying: preparation, characterization, and dissolution profiles. AAPS PharmSciTech. 2009;10(2):391-401.
[53]. Mauludin R, Müller RH. Physicochemical properties of hesperidin nanocrystal. Int J Pharm Pharm Sci. 2013;5(Suppl 3):954-60.
[54]. Morsy MA, Nair AB. Prevention of rat liver fibrosis by selective targeting of hepatic stellate cells using hesperidin carriers. Int J Pharm. 2018;552(1-2):241-50.
[55]. Tsirigotis-Maniecka M, Lamch Ł, Chojnacka I, Gancarz R, Wilk KA. Microencapsulation of hesperidin in polyelectrolyte complex microbeads: Physico-chemical evaluation and release behavior. J Food Eng. 2017;214:104-16.
[56]. Kalita B, Patwary BN. Formulation and In Vitro Evaluation of Hesperidin-Phospholipid Complex and its Antioxidant Potential. Curr Drug Ther. 2020;15(1):28-36.
[57]. Bhalerao RA, Bhalekar MR, Damle MC. Formulation and Evaluation Transdermal Patch of Hesperidin. Journal of Drug Delivery and Therapeutics. 2019;9(4):311-7.
[58]. Li Y, Kandhare AD, Mukherjee AA, Bodhankar SL. Acute and sub-chronic oral toxicity studies of hesperidin isolated from orange peel extract in Sprague Dawley rats. Regulatory Toxicology and Pharmacology. 2019;105:77-85.