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Formulation and Evaluation of Traditional Antioxidant Grape Seeds Extract in the Form of Tablets

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ABSTRACT

Oxygen uptake while breathing cause's free radical production and in addition to that environmental factors such as pollutants, smoke and certain chemicals also contribute to their formation. Reactive oxygen species is a collective term that includes all reactive forms of oxygen, including both oxygen radicals and several non-radical oxidizing agents that participate in the initiation and/or propagation of chain reaction. Free radicals are atoms, molecules or ions with unpaired electrons that are highly unstable and active towards chemical reactions with other molecules. Antioxidant is any substance that when present at low concentrations compared to those of an oxidizable substrate significantly delays or prevents oxidation of that substrate. Antioxidants block the process of oxidation by neutralizing free radicals. Antioxidant power of proanthocyanidins is 20 times greater than vitamin E and 50 times greater than vitamin C. Proanthocyanidins in Grape seeds have been shown to exhibit strong antioxidant, antimutagenic, anti-inflammatory, anticarcinogenic and antiviral activity.

Keywords- Antioxidants, Grape seed, Proanthocyanidins, DPPH activity.

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INTRODUCTION-

Oxygen is an indispensable element for life, under certain situations has severe deleterious effects on the human body. The negative effects of oxygen are due to the formation and activity of number of chemical compounds, known as reactive oxygen species (ROS). Reactive oxygen species is a collective term that includes all reactive forms of oxygen, including both oxygen radicals and several non-radical oxidizing agents that participate in the initiation and/or propagation of chain reaction.[1] Oxygen uptake while breathing causes free radical production and in addition to that environmental factors such as pollutants, smoke and certain chemicals also contribute to their formation. In turn, these radicals can start chain reactions in cells and it can cause damage or death to the cell. Chemical compounds capable of generating potential toxic oxygen species can be referred to as 'Pro-oxidants.' In normal cell, there is an appropriate pro-oxidant-antioxidant balance. However, this balance can be shifted towards pro-oxidants when production of oxygen species is increased greatly or when level of antioxidants are diminished. This stage is called as 'oxidative stress'.[2]

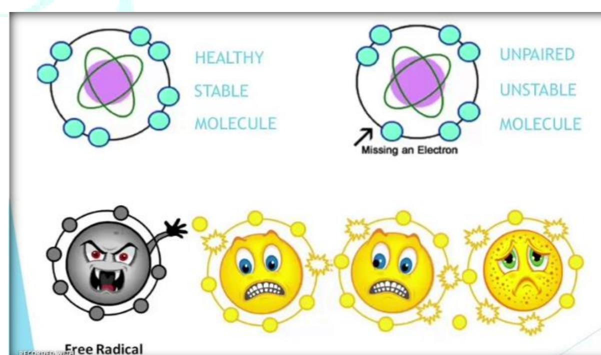

Fig. No: 01 Effect of free radicals on body tissue

The most common oxidants in biological systems are free radicals. Free radicals are atoms, molecules or ions with unpaired electrons that are highly unstable and active towards chemical reactions with other molecules. Free radicals are parts of groups of molecules called reactive oxygen species (ROS), reactive nitrogen species (RNS) and reactive sulphur species (RSS).[3]

Free radicals can be formed in 3 ways, (i) by hemolytic cleavage of covalent bond of a normal molecule, with each

fragment retaining one of the paired electrons, (ii) by loss of single electron from normal molecule and (iii) by addition of a single electron to a normal molecule.[4]

Table No: 01 Sources of Free Radicals

S. N.	Endogenous Sources	Environmental Sources
1.	Mitochondrial leak	Cigarette smoke
2.	Respiratory burst	Pollutants
3.	Enzyme reactions	UV light
4.	Auto oxidation reaction	Ionizing radiation
5.		Xenobiotics

During environmental stress and cell dysfunction, ROS levels can increase dramatically, and cause significant cellular damage in the body. Thus, oxidative stress significantly contributes to the pathogenesis of inflammatory disease, cardiovascular disease, cancer, diabetes, Alzheimer's disease, cataracts, autism and aging.[5]

Antioxidants and Their Mechanism of Action-

Antioxidant is any substance that when present at low concentrations compared to those of an oxidizable substrate significantly delays or prevents oxidation of that substrate. This is a broader definition encompassing many vulnerable macromolecules (e.g. DNA, lipids and proteins) that can be affected by oxidation. Antioxidants can also be defined as substances that trap harmful forms of oxygen and prevent them from damaging cells. Mechanistic definitions of antioxidants are usually focused on the ability to be a hydrogen donor or an electron donor.[6] Antioxidants block the process of oxidation by neutralizing free radicals. In doing so, the antioxidants themselves become oxidized. The two possible pathways are chain-breaking and preventive.[7]

Antioxidants are effective because they are willing to give up their own electrons to free radicals. When a free radical gain the electron from an antioxidant it no longer needs to attack the cell and the chain reaction of oxidation is broken. After donating an electron an antioxidant becomes a free radical by definition. Antioxidants in this state are not harmful because they have the ability to accommodate the change in electrons without becoming reactive.[8]

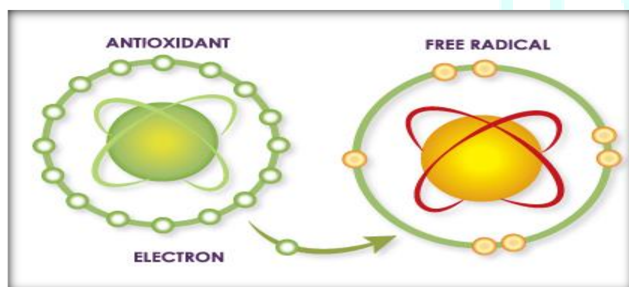

Fig. No: 02 Antioxidant Process

Benefits of Herbal Antioxidants over the Synthetic Antioxidants-

Synthetic antioxidants such as Butylated hydroxytoulene (BHT) and Butylated Hydroxyanisole (BHA) reported with symptoms included vasomotor rhinitis, headache, flushing, asthma, conjunctival suffusion, dull retrosternal (behind the breastbone) pain radiating to the back, diaphoresis (excessive sweating), or somnolence (sleepiness). These synthetic antioxidants have been found to cause dermatitis in a number of people contact dermatitis was caused by TBHQ in a hair dye and cross sensitization with BHA and BHT was noted. "BHT may convert to other substances in the human body that may be carcinogenic." Consumption of polyphenolic-rich foods has also been linked to a decreased risk for certain cancers such as lung, breast, esophageal, ovarian, stomach, and colon. Antioxidant power of proanthocyanidins is 20 times greater than vitamin E and 50 times greater than vitamin C.[9]

Proanthocyanidins in grape seeds have been shown to exhibit strong antioxidant, antimutagenic, anti-inflammatory, anticarcinogenic and antiviral activity and scavenge reactive oxygen and nitrogen species, modulate immune function and platelet activation, and produce vasorelaxation by inducing nitric oxide (NO) release from endothelium.[10]

MATERIALS AND METHOD-

Materials:

The materials used for the Grape seed extract tablets were Grape seed Extract gifted by the Sunpure Pvt. Ltd. Lactose used as binder, Gum acacia and HPMC used as a binder, starch and crospovidone as a disintegrating and super disinteganting agent respectively, Talc and Magnessium stearate as a glident and lubricant.

FORMULATION AND EVALUATION OF TABLETS:

1) Precompressional Evaluation Study of Powder:- [11]

a. Bulk density:

The bulk density was measured by using cylinder and measuring the volume and weight.

b. Tapped density:

Tapped density was determined by placing a graduated cylinder containing a known mass of drug on a mechanical tapper apparatus which was operated at fixed number of taps until the powder bed volume had reached to minimum. The unit of tapped density and untapped density is reported in g/ml. Bulk density was calculated using the following formula.

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume of powder}}$$

$$\text{Tappeddensity} = \frac{\text{Weightofpowder}}{\text{Tappedvolumeofpowder}}$$

c. Compressibility index-

The interparticulate interactions influencing the bulking properties of a powder are also the interactions that interfere with powder flow, a comparison of the bulk and tapped densities can give a measure of the relative importance of these interactions in a given powder. Such a comparison is often used as an index of the ability of the powder to flow, for example the Compressibility index or Hausner's ratio.

Table No: 02 Relationship between % compressibility and flow ability

% Compressibility	Flow ability
5-15	Excellent
12-16	Good
18-21	Fair To Passable
23-35	Poor
33-38	Very Poor
>40	Extremely Poor

Formula for % Compressibility Index-

$$\%\ \text{Compressibility Index} = \left[1 - \frac{V}{V_0}\right] \times 100$$

Where, V and V_0 are the volumes of the sample after and before the standard tapping respectively.

REF-

2) Formulation of Tablets:-

1. Preparation of mixed blend of drug and excipients-

All the ingredients were passed through mesh no. 60. Required quantity of ingredients was weighed as given in Table 2 and coground in mortar and pestle. The powder blend was evaluated for flow property and compressibility behavior.

2. Compression of Tablets-

Grape seed extract tablets were prepared by direct compression method using various formulation additives in varying concentrations and the detailed composition was shown in the Table 2. All the ingredients were powdered separately in a clean and dry porcelain mortar and then they were passed through # 60 mesh sieve. The drug and the additives were mixed thoroughly in an inflated polyethylene pouch in a geometric ratio of their weight. Then the powder mixture was compressed in to tablets of 300 mg weight using 6 mm flat round punches.

Table No. 03 Formulation Table of Tablets

Ingredient(mg)/Formulation	F1	F2	F3	F4	F5	F6	F7	F8
Grape seed extract	200	200	200	200	200	200	200	200
Lactose	65	65	65	65	65	65	65	65
Gum Acacia	15	-	18	-	18	-	18	-
HPMC	-	15	-	18	-	18	-	18
Starch	12	12	12	12	-	-	-	-
Crosspovidone	-	-	-	-	12	12	12	12
Talc	3	3	3	3	3	3	3	3
Magnessium stearate	2	2	2	2	2	2	2	2

3) Evaluation of Tablets:- [12, 13, 14]

1) Tablet thickness and size:-

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using Vernier Callipers.

2) Hardness:-

Hardness exhibits tensile strength of tablet. The force needed to fracture the tablet by diametric compression is referred as crushing strength of tablet. Hardness is a deformation property of solid. The hardness of the six tablets from each formulation batch was determined using Monsanto hardness tester.

3) Friability:-

Friability is the measure of tablet strength. Roche type friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

Formula for friability-

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

4) Uniformity of weight:-

Table no: 04 Standard values for uniformity of weight

Average weight of Tablet (mg)/ IP/BP	Maximum percentage of deviation allowed (%)
80 or less	10
80-250	7.5
More than 250	5

Twenty tablets were taken and their weight was determined individually and collectively using single pan electronic balance. The average weight of the tablets was determined from collective weight. From the individual tablet weight, the range and percentage deviation was calculated Not more than 2 tablets should deviate from the average weight of tablet and maximum percentage of deviation allowed.

5) Disintegration study-

In the disintegration time study, six tablets were tested. Each tablet was put into 900 ml HCL solution (0.1N) at 37±2^{0}C. Time required for complete dispersion of a tablet was measured with the help of disintegration test device.

6) Dissolution Study-

All the tablet dissolution studies were carried out for three tablets (triplicate) per formulation. USP Type II dissolution apparatus was used for drug release studies.

Table No. 05 Parameters were used in release study

Sr. No.	Speed of paddle	100 rpm
1.	Temperature	37±0.5°C
2.	Sampling time	3 hrs
3.	Volume drawn	10 ml
4.	Dilution factor	10
5.	Volume of dissolution medium	900 ml
6.	Dissolution medium	1M HCL P^H 1.5
7.	Spectrophotometric analysis	UV-Visible at 280 nm

7) 1, 1-diphenyl-2-picrylhydrazyl (DPPH) Radical scavenging activity:-[15]

An Aliquot of 3ml of 0.004% DPPH solution in methanol and 0.1 ml of plant extract at various concentrations (20, 40, 60, 80, 100, 120, 140, 160, 180 and 200ug/ml) were mixed. The mixture was shaken vigorously and allowed to reach a steady state at room temperature for 30 minutes. Decolorization of DPPH was determined by measuring the absorbance at 517nm. A control was prepared using 0.1 ml of respective vehicle in the place of plant extract/ ascorbic acid. The

%inhibition activity was calculated by using the following formula.

Formula for DPPH activity-

$$\% \text{ Inhibition} = \frac{\text{Absorbance of control} - \text{Absorbane of GSE/Ascorbic Acid}}{\text{Absorbance of control}} \times 100$$

RESULTS AND DISCUSSION-

The precompressional evaluation study was evaluated on grape seed extract powder and the all ranges are within limit.

Table No: 06 Flow properties of Grape seed extracts powder

Sr. No.	Parameters	Observations
1.	Bulk density(gm/ml)	0.57
2.	Tapped density(gm/ml)	0.74
3.	Angle of repose	11.08^0
4.	Compressibility index (%)	22.90
5.	Hausner's ratio	1.2

The prepared tablets of batch F5 were spherical, smooth surface with homogenized evenly distributed colored, having 300mg dose. The tablets are evaluated in all the tablet evaluation parameters. The maximum weight variation of the F5 tablets was ±7.5%, hence the tablets of batch F5 passed the weight variation test.

Hardness for tablets of batch F5 was in the range of [5.76-13.5 kg/cm^2], which falls above the limit of not less than 5 kg/cm^2. Friability value for tablets of the batch F5 was 0.338% which is lower than 1%. Disintegration time is an important parameter of tablets as it's the first stage for active ingredients to be released. In this study, the tablets of batch F5 disintegrated within 5 minutes which is a less than the ideal disintegration time that is within 15 minutes for tablets and the dissolution test for F5 batch of tablet releases 99.05% drug release within 2 hours.

The IC_{50} value and correlation coefficient (R^2) of GSE by DPPH radical scavenging activity were calculated from the graph and is represented in Table no. 35. GSE had an IC_{50} value of 46.01 and R^2 0.950 which was comparable with ascorbic acid which had an IC_{50} 38.01 and R^2 0.907. GSE, thus, showed significance enhancement of DPPH radical.

Table no: 07 DPPH free radical scavenging activity of GSE and Ascorbic acid

Concentration (µg/ml)	% Inhibition of DPPH radical		IC_{50}	
	GSE	Ascorbic acid	GSE	Ascorbic acid
05	29.84	27.48	46.01	38.01
10	39.49	52.04		
30	61.28	83.04		
50	79.9	87.13		
80	107.83	105.97		

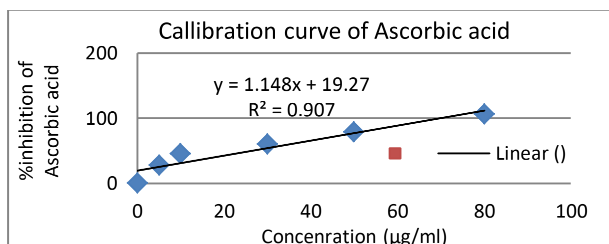

Fig. No: 03 DPPH scavenging radical activity of Ascorbic acid

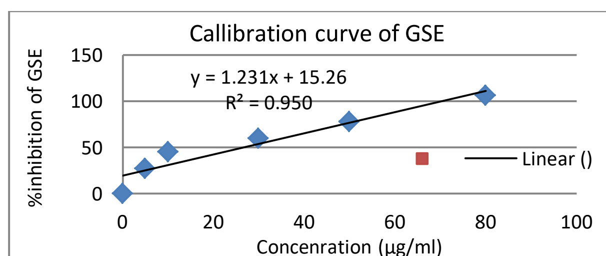

Fig. No: 04 DPPH scavenging radical activity of GSE

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