COMPARATIVE ANTIOXIDANT POTENTIAL OF HYLOCEREUS UNDATUS, LITCHI CHINENSIS AND SYZYGIUM JAMBOS: AN IN VITRO STUDY

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Abstract:
To study the antioxidant anti inflammatory property of selected fruit extracts of *Hylocereus undatus*, *Litchi chinensis* and *Syzygium jambos* using different model systems. The antioxidant potential was estimated by using hydroxyl radical, DPPH radical scavenging activities, hydrogen peroxide assay HRBC assay and albumin denaturation assay. The *Litchi chinensis* reported to have superior activity on hydroxyl radical, DPPH radical, and albumin denaturation assay and *Hylocereus undatus* reported to have hydrogen peroxide and HRBC stabilization assay. The antioxidant and anti-inflammatory activities might be due to the polyphenols present in the selected fruits.

Keywords: Fruits, Antioxidants, Anti-inflammatory, Polyphenol

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Introduction:

The modern lifestyle associated with an unhealthy diet, lack of physical exercise, exposure to a combination of chemicals from different sources pesticides, heavy metals, food additives, and environmental pollution can influence the appearance of oxidative stress (Tsatsakis AM et al., 2019). It can contribute to the increasing burden of chronic diseases, as is suggested by several experimental and human studies**.** Polyphenols are natural compounds present in plants with numerous biological activities. Phenolic compounds and flavonoids can interact with ROS/RNS and thus terminate chain reaction before cell viability is seriously affected (Kumar S., 2013). The excessive production of ROS may cause tissue injury that may lead to the inflammatory process. Polyphenol antioxidant activity depends on the structure of their functional groups. The number of hydroxyl groups greatly influences several mechanisms of antioxidant activity such as scavenging radicals and metal ion chelation ability (Willcox JK., 2004).

Polyphenol antioxidant activities are related to their capacity to scavenge a wide range of ROS. Indeed, the mechanisms involved in the antioxidant capacity of polyphenols include suppression of ROS formation by either inhibition of enzymes involved in their production, scavenging of ROS, or up regulation or protection of antioxidant defenses. It is important to mention that many polyphenolic compounds are in fruits bound to sugars (glycosylated), such as glucose, galactose, xylose, rhamnose, and others, and methylates whose bioavailability in the organism is modified depending on these groups (Gerard Bryan G et al., 2015). The phenolic groups in polyphenols can accept an electron to form relatively stable phenoxyl radicals, thereby disrupting chain oxidation reactions in cellular components (Clifford MN., 2000). Evidences for fruit are rich source of polyphenols and indicates these compounds may confer anti-inflammatory and/or inflammatory response stabilizing activities, which would have important implications in health maintenance and disease risk reduction (Joseph SV., 2016). The present study was designed to evaluate antioxidant and anti-inflammatory effect of selected fruits such as *Hylocereus undatus*, *Litchi chinensis*, and *Syzygium jambos* using *in vitro* methods.

Materials and Methods:

Plant extracts: The selected fruits are obtained from local areas of Guntur, Andhra Pradesh. The obtained fruits were authenticated by Dr. P Satyanarayana Raju, Dept of botany and microbiology, Acharya Nagarjuna University.

Chemicals and reagents:

NaH_2PO_4, Na_2HPO_4 and hydrogen peroxide, Sodium nitroprusside, Sulfanilamide, Napthyl ethylene diamine hydrochloride, Phosphoric acid were purchased from Sisco Research Laboratories, Mumbai. 1, 1 -diphenyl-2-picrylhydrazyl**,** ethanol were purchased from S.D Fine Chemicals, Mumbai.

Methods:

Hydrogen Peroxide Scavenging Activity: The hydrogen peroxide scavenging assay was carried out following the procedure of Ruch et al., 1989. The principle of this method is that there is a decrease in absorbance of H_2O_2 upon oxidation of H_2O_2. A solution of 43 mM H_2O_2 was prepared in 0.1M phosphate buffer (pH 7.4). The purple heart and riboflavain of different concentrations were prepared in 3.4 mL phosphate buffer were added to 0.6 mL of H_2O_2 solution (43 mM) and absorbance of the reaction mixture was recorded at 230 nm. All experiments were performed in triplicates and percent inhibition activity was calculated

DPPH Radical Scavenging Activity: The potential of extract and riboflavin was determined on the basis of the scavenging activity of the stable 1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical. Aliquots of 1ml of a methanolic solution containing each concentration of extract were added to 3 ml of 0.004% MeOH solution of DPPH. Absorbance at 517 nm, against a blank of methanol without DPPH, was determined after 30 min (UV, Perkin-Elmer-Lambda 11 spectrophoto- meter) and the percent inhibition activity was calculated (Braca et al., 2001).

The human red blood cell (HRBC) membrane stabilization method:

The method has been used as a method to study the in vitro anti-inflammatory activity (Gandhisan R, ., 1991). The blood was collected from healthy human volunteer who had not taken any NSAIDS for 2 weeks prior to the experiment and mixed with equal volume of Alsever solution(2 % dextrose, 0.8 % sodium citrate, 0.5 % citric acid and 0.42 % NaCl). All the blood samples were stored at 4 °C for 24 h before use. It was centrifuged at 2500 rpm for 5 min and the supernatant was removed. The cell suspension was washed with sterile saline solution (0.9 % w/v NaCl) and centrifuged at 2500 rpm for 5 min. This was repeated three times till the supernatant was clear and colorless and the

packed cell volume was measured. The cellular component was reconstituted to a 40 % suspension (v/v) with phosphate buffered saline (10 mM, pH 7.4) and was used in the assays.

Albumin denaturation inhibitory activity

The assay was carried out by adopting the methods described by Kumari *et al*. 2015 with some modifications in which the volume of each component in the reaction mixtures was reduced by half. The plant extracts and positive standards (ibuprofen and diclofenac) were prepared at a concentration of 0.1% each (1.0 mg/ml). A reaction vessel for each mixture was prepared consisted of 200 µl of egg albumin, 1400 µl of phosphate buffered saline, and 1000 µl of the test extract. Distilled water instead of extracts was used as a negative control. Afterward, the mixtures were incubated at 37°C for 15 min and then heated at 70°C for 5 min. After cooling, their absorbances were measured at 660 nm

Results and Discussion:

Table 1: Effect of selected extracts and ascorbic acid on Hydroxyl radical scavenging activity

Concentrations (µg/ml)	**L-AA**	**HAFHU**	**HAFLC**	**HAFSJ**
10	23.18±1.16	19.99±0.40	18.27±0.21	11.63±0.49
20	34.54±0.53	28.09±0.54	26.82±0.29	14.17±0.29
30	42.46±0.38	37.48±0.22	33.12±0.29	27.21±0.35
40	51.02±0.67	45.67±0.48	38.93±0.40	35.69±0.30
50	60.22±0.24	54.49±0.59	50.30±0.38	40.71±0.28
100	87.67±0.61	81.10±0.36	76.79±0.29	70.02±0.41
R^2	0.977	0.980	0.988	0.980
IC50	**41.88**	56.11	**49.92**	66.96

Each value represents the mean ± SEM (n = 3).

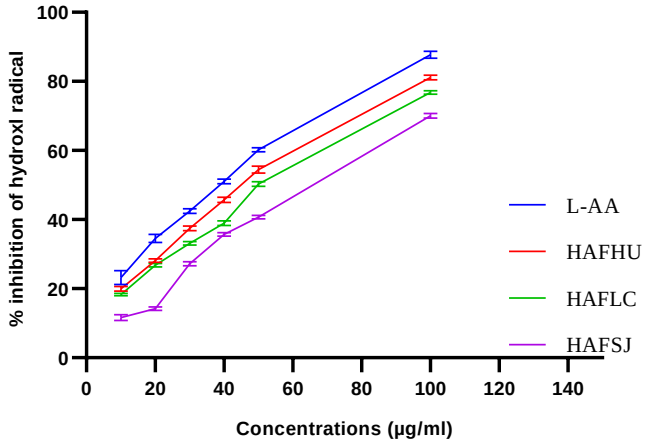

Figure 1: Effect of selected extracts and ascorbic acid on Hydroxyl radical scavenging activity

Table 2: Effect of selected extracts and ascorbic acid on Hydrogen peroxide scavenging activity

Concentrations (µg/ml)	**L-AA**	**HAFHU**	**HAFLC**	**HAFSJ**
1	33.00±0.45	28.08±0.44	20.27±0.38	19.80±0.32
2	47.15±0.40	36.64±0.31	28.37±0.25	32.79±0.34
4	62.12±0.48	54.05±0.45	46.40±0.38	47.15±0.48
6	72.76±0.52	63.81±0.26	57.62±0.70	64.86±0.36
8	82.42±0.56	72.93±0.38	74.40±0.39	71.35±0.31
10	92.36±0.55	84.54±0.37	90.94±0.17	84.31±0.40
R^2	0.970	0.983	0.997	0.976
IC50	**2.77**	**4.07**	4.78	4.68

Each value represents the mean ± SEM (n = 3).

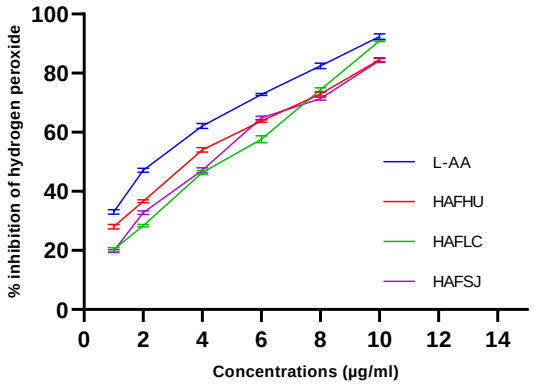

Figure 2: Effect of selected extracts and ascorbic acid on Hydrogen peroxide scavenging activity

Table: Effect of selected extracts and ascorbic acid on DPPH radical scavenging activity

Concentrations (µg/ml)	**L-AA**	**HAFHU**	**HAFLC**	**HAFSJ**
50	33.21±0.76	21.65±0.34	32.76±0.29	18.96±0.17
100	42.83±0.17	33.82±0.43	42.61±0.38	24.10±0.27
200	53.93±0.40	43.32±0.15	50.72±0.27	38.28±0.48
300	60.77±0.33	51.44±0.63	58.78±0.42	47.14±0.49
400	72.75±0.46	61.20±0.56	67.30±0.40	56.35±0.44
500	85.67±0.33	76.16±0.50	76.20±0.80	70.30±0.39
R^2	0.989	0.987	0.981	0.994
IC50	**185.04**	278.72	**206.92**	326.57

Each value represents the mean ± SEM (n = 3).

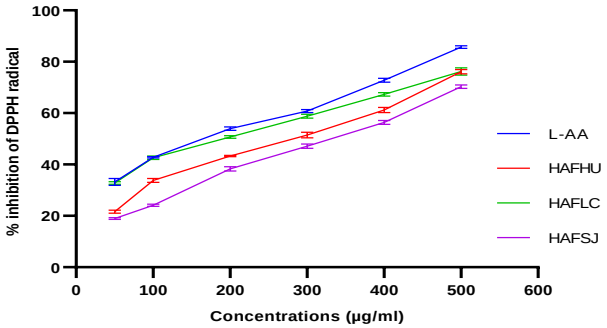

Figure: Effect of selected extracts and ascorbic acid on DPPH radical scavenging activity

Table: Effect of selected extracts and Diclofenac on HRBC membrane stabilization assay

Concentrations (µg/ml)	**Diclofenac**	**HAFHU**	**HAFLC**	**HAFSJ**
100	31.15±0.27	38.14±0.26	22.21±0.52	18.44±0.45
200	42.07±0.39	55.47±0.39	36.51±0.23	22.29±0.64
300	65.51±0.35	64.18±0.29	47.42±0.49	39.46±0.54
400	76.52±0.55	73.03±0.39	54.29±0.72	58.91±0.40
500	96.03±0.40	85.74±0.60	71.74±0.47	67.01±1.04

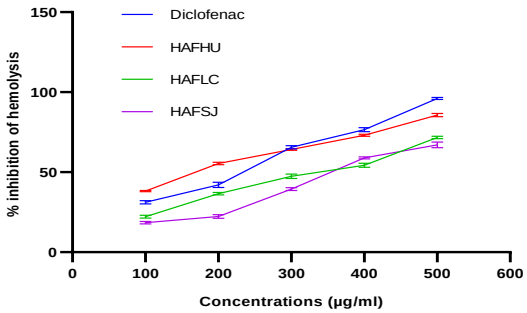

Figure: Effect of selected extracts and Diclofenac on HRBC membrane stabilization assay

Table: Effect of selected extracts and Diclofenac on albumin denaturation Assay

Concentrations (µg/ml)	Diclofenac	HAFHU	HAFLC	HAFSJ
100	28.12±1.00	10.39±0.29	23.23±0.53	11.43±0.35
200	38.43±0.60	19.71±0.44	32.39±0.47	22.11±0.68
300	55.16±0.61	38.21±0.45	45.23±0.70	42.65±1.24
400	76.56±0.57	54.50±0.73	67.48±0.59	53.99±0.20
500	84.31±0.55	76.30±0.50	79.22±0.55	65.58±0.54
R^2	0.980	0.984	0.979	0.987
IC50	257.6	362.40	318.64	377.85

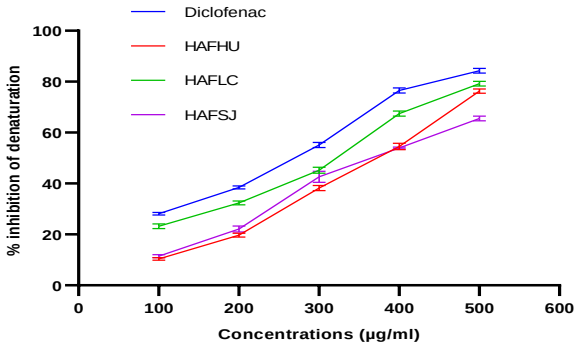

Figure: Effect of selected extracts and Diclofenac on albumin denaturation Assay

Discussion:

Oxidative stress involves the chemistry of reactions of so-called reactive species derived from oxygen and nitrogen. Free radicals are usually destroyed by our body's natural antioxidant system. The free radicals can trigger a negative chain reaction in the body, a reaction that can destroy the cell membrane, block the action of major enzymes, prevent cellular processes necessary for the proper functioning of the body, prevent normal cell division, destroy deoxyribonucleic acid (DNA), and block energy generation (Kurutas, 2015). Oxidative stress is reported to associate with the development of several metabolic, chronic disorders or cancers (Aminjan et al., 2019). For example, scavenging of hydroxyl radical (•OH) is impractical, but preventing its formation by reducing hydrogen peroxide (H_2O_2) production can provide effective prevention of damage (Forman HJ., 2010). One of the major misunderstandings in the field of oxidative stress concerns the scavenging of superoxide ($O_2^{\bullet-}$) or H_2O_2 by small molecules, which are also ineffective inside cells (Ansari MA., 2010).

Oxidants, particularly H_2O_2 generated by cells upon physiological stimulation, can act as second messengers. Also, the increase in H_2O_2 production and iron release from proteins in oxidative stress by $O_2^{\bullet-}$ and $ONOO^-$ causes a marked elevation in the production of lipid peroxidation products including 4-hydroxy-2-nonenal (HNE), which can also cause aberrant signaling (Matsushima S., 2014). ROS homeostasis is ensured by various antioxidant systems present both in plants (Sharma et al., 2012) and in the human body. Vitamin C (ascorbic acid) exists in two redox forms: ascorbic acid (AA) is the reduced form, which is deprotonated at physiological pH (thus, occurring in its anion form, ascorbate) (Birben et al., 2012).

Due to its high electron-donating power, AA can undergo two-electron oxidation, yielding dehydroascorbic acid (DHA) (Kocot et al., 2017). Humans do not express the enzyme L-gluconolactone oxidase, avoiding the possibility of endogenous synthesis. Thus, AA must be ingested through food (or supplements), particularly tomatoes, pineapples, watermelons, and all citrus fruits (Banafsheh and Sirous, 2016). Ascorbic Acid is the principal biologically active form but Dehydroascorbic acid, an oxidation product also shows biological activity. AA effectively quenches ROS, both directly and cooperatively regenerating oxidized vitamin E, GSH, and carotenoids. Scavenged ROS can be superoxide anion, $^1O_2$, H_2O_2, organic peroxides, ●OH, or hypochlorous acid (HClO). Many fruits are high in antioxidants, packed with vitamins, and beneficial in a myriad of ways. These include cranberries, red grapes, peaches, raspberries, strawberries, red currants, figs, cherries, pears, guava, oranges, apricots, mango, red grapes, cantaloupe, watermelon, papaya, and tomatoes. These function as free

radical scavengers, singlet and triplet oxygen quenchers, enzyme inhibitors, peroxide decomposers, and synergists (Adewale A., 2015). Hence, the present study is designed to evaluate the role of fruits in free radical scavenging activity and anti-inflammatory activity using in vitro models.

In living organisms, there are two major reactive oxygen species, superoxide radical and hydroxyl radical that are continuously formed in a process of reduction of oxygen to water. The hydrogen peroxide in the Fenton reaction led to the misleading concept of oxidative stress that ignores the fact that hydroxyl radical, is known to be the most biologically active free radical (Davies KJA., 2000). The flavonoids can promote ROS formation by reacting with H2O2 and generating highly reactive •OH, in a series of Fenton and Fenton-like reactions. Indeed, flavonoids have the well-known capacity to chelate several metal ions (such as iron and copper), blocking free radical generation (Kumar and Pandey, 2013). The order of potency of hydroxyl radical scavenging activity was L-AA> HAFLC>HAFHU> HAFSJ. Among selected fruits, the *Litchi chinensis* was found to show potent hydroxyl radical scavenging activity as shown in table 1. H_2O_2 received considerable interest among ROS and other oxygen-derived free radicals. A comparatively long life span and the small size of H_2O_2 molecules permit them to traverse through cellular membranes to different cellular compartments, facilitating signaling functions, including retrograde signaling (Noctor et al., 2014). The order of potency of hydrogen peroxide scavenging activity was found to be L-AA>HAFHU>HAFLC>HAFSJ. The *Hylocereus undatus was* shown to have superior hydrogen peroxide scavenging activity among other fruits as shown in table 2.

Antioxidants (AH) or other radical species ($R^{\bullet}$) can react with this stable radical ($DPPH^{\bullet}$) by providing an electron or hydrogen atom, thus reducing it to 2,2-diphenyl-1-hydrazine (DPPH-H) or substituted analogous hydrazine (DPPH-R) characterized by colorless or pale-yellow color which could be easily monitored with a spectrophotometer (Szerlauth A., 2019). Henceforth, this compound is usually used in DPPH assay for the determination of the antioxidant activity of medicinal plants, fruits, or any other biological substrates. The solution loses color with the increase in the concentration of antioxidants as the electrons are taken up by the DPPH radical from the antioxidant. The potency of selected extracts was found to be more with *Litchi chinensis* and the order of potency was L-AA> HAFLC>HAFHU> HAFSJ.

Free radicals cause inflammation in humans through cellular damage. Chronic inflammation produces lots of free radicals which ultimately create more inflammation. This continuous vicious cycle can damage many systems in the human body (Silpak B., 2017). The role of free radicals can be found in the inflammatory process which is a complex process resulting in many human diseases. Inflammations are mainly divided into acute and chronic inflammation depending on various inflammatory processes and cellular mechanisms. At the onset of an inflammation, the cells undergo activation and release inflammatory mediators (Ferrero-Miliani L., 2007). HRBC method was selected for the *in vitro* evaluation of anti-inflammatory properties because the erythrocyte membrane is analogous to the lysosomal membrane and the stabilization of the lysosomal membrane is important in limiting the inflammatory response by preventing the release of lysosomal constituents of activated neutrophil, such as bactericidal enzymes and proteases, which cause further tissue inflammation and damage upon extra cellular release (Shenoy S., 2010). The order of potency to stabilize the HRBC membrane was found to be L-AA>HAFHU>HAFLC>HAFSJ.

Membrane stabilization leads to the prevention of leakage of serum protein and fluids into the tissues during a period of increased permeability caused by inflammatory mediators (Chaitanya R., 2011). The extracts perhaps stabilized the red blood cell membrane by preventing the release of lytic enzymes and active mediators of inflammation. Protease inhibitors also play an important role in the better interpretation of the basic principle of protein interaction. It has been previously reported that leukocyte protease plays important role in the development of tissue damage during inflammatory reactions and a significant level of protection was provided by protease inhibitors (Kajay TD., 2006). To identify the protection offered by the selected fruits using albumin denaturation assay and was found to be L-AA> HAFLC>HAFHU> HAFSJ.

The significant actions of selected extracts might be due to the presence of active phytochemicals responsible for antioxidant and anti-inflammatory actions. The Hylocereus undatus fruit contains betalains, polyphenolic compounds (gallic acid and betacyanins), and carotenoids. Anthocyanins can be found in the skin of H. undatus, including

cyanidin 3-O-glucoside, cyanidin 3,5-O-glucoside, and pelargonidin 3,5-O-glucoside cyanidin 3-O-glucoside were also identified in the peel of dragon fruit (De Mello FR., 2015). The high level of vitamin C found in Dragon fruit plays an important role to enhance the immune system and also to stimulate the activity of other antioxidants in the body (Gunasena H., 2010). Litchi chinensis fruit contains epicatechin; procyanidin A2 and procyanidin B2; leucocyanidin; cyanidin glycoside, malvidin glycoside, and saponins; butylated hydroxytoluene; isolariciresinol; kaempferol; rutin; and stigmasterol (Eswar Kumar K., 2016). Litchi fruit phenolics strongly inhibited linoleic acid oxidation and exhibited a dose-dependent free-radical scavenging activity against DPPH and hydroxyl radicals and superoxide anions. The degradation of deoxyribose by hydroxyl radicals was inhibited by phenolics acting mainly as iron ion chelators, rather than by directly scavenging the radicals (Xuewu D., 2007). Litchi pericarp was reported for superoxide, hydroxyl, hydrogen peroxide, and nitric oxide radical scavenging activities and also demonstrated for Fe+2 chelating activity, ferric reducing antioxidant power (FRAP) and Trolox equivalent antioxidant capacity (TEAC) (Eswar Kumar K., 2017). The flavonol glycosides and flavones as well as ellagitannins and phenolic acids, Gallic, caffeic and chlorogenic acids, as well as rutin, quercetin, and kaempferol as bioactive compounds in the extracts *Syzygium jambos.* exhibited a total antioxidant activity with an ascorbic acid equivalent of 142.32 μg/mL (Jobina R, Madhu D., 2018); *Syzygium jambos* presented thiol-peroxidase like activity; free radical scavenger of DPPH radical, reducing total phenol capacity, total flavonoid content, and total antioxidant capacity (Mansour S., 2018).

Conclusions: The potency of three selected fruits with standard ascorbic acid was studied and observed that *Litchi chinensis* was reported to have superior activity on hydroxyl radical, DPPH radical, and albumin denaturation assay and *Hylocereus undatus* reported to have hydrogen peroxide and HRBC stabilization assay. All the reported actions might be due to the respective phytochemicals present in the fruits.

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