ANTIOXIDANT AND IN VIVO ANTI-INFLAMMATORY POTENTIAL OF EXTRACT OF MORINDA CITRIFOLIA FRUIT AND STEM

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Abstract:
Morinda citrifolia (Family: Rubiaceae) have been used since ancient times in the traditional medicinal systems like, Ayurveda, Siddha, Chinese and many other system of medicines in the treatment of various ailments. The fruits have been used topically in various conditions like, sprains, swellings, wounds and bruises. In present work Phytochemical and Pharmacological Evaluation of various Extract of Morinda Citrifolia fruit and stem were performed t proves as Anti-Inflammatory Agent. In India, abundant precious plants are used in Ayurveda as well as traditionally for the treatment of inflammation. The discovery of inflammatory inhibitors from natural origin will present an opportunity for a medicinal chemist to design novel, structurally diverse selective inflammatory inhibitors. The present study was undertaken based on the ethno medical background of the plants such as *Morinda citrifolia* Fruit and stem part of these plants were selected for anti inflammatory activity. Methanol extract of M. citrifolia fruit extract at 400 µg/ml concentrations displayed 50.2±0.73, maximum activity compared to other all extracts. Methanol extract of Morinda citrifolia fruit stem (MMCF, MMCS) were evaluated for carrageenan-induced hind paw edema is the standard experimental model of acute inflammation. The carageenan-induced paw edema model in rats is known to be sensitive to cyclooxygenase (COX) inhibitors and has been used to evaluate the effect of non-steroidal anti-inflammatory agents, which primarily inhibit the COX involved in prostaglandin synthesis. In carrageenan induced rat paw edema method methanol extract of M. citrifolia fruit showed significant decrease in paw edema volume. The results were compared to the standard Indomethacin. MMCF at the dose of 400 mg/kg showed a maximum inhibition of 74.51 % upto 4 h while the standard showed an inhibition of 78.11%. The percentage inhibition of rat paw edema of the Methanol extract of M. citrifolia fruit showed significant decrease in paw edema volume. The results were compared to the standard Indomethacin. MMCS at the dose of 400 mg/kg showed a maximum inhibition of 64.51 % upto 4 h while the standard showed an inhibition of 81.12 %.

Keywords: Antiinflammatory Activity, *Morinda citrifolia fruits*, Methanolic extracts

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Introduction:

Inflammation is a major factor for the progression of various chronic diseases/disorders, including diabetes, cancer, cardiovascular diseases, eye disorders, arthritis, obesity, autoimmune diseases, and inflammatory bowel disease. Free radical productions from different biological and environmental sources are due to an imbalance of natural antioxidants which further leads to various inflammatory diseases **[1]**. In the recent years, inflammation is one of the major target research areas among biomedical researchers, which includes various cellular processes (e.g., phagocytosis, chemotaxis, mitosis, and cell differentiation). There are several studies described on how the immune system (cellular immunity and antibodies) leads to an inflammatory response, and there is an additional huge clinical literature about individual steps in inflammation **[2]**. Inflammation is a vital response of human immune system. Nevertheless, the state of chronic inflammation can have several secondary consequences in biological response associated with enhanced risk of chronic diseases and disorders. Chronic inflammation in tissue usually happens when inflammatory responses are in the absence of an actual stimulus **[3]**. It usually occurs through infections that are not resolved either within endogenous protection mechanisms or via some other resistance mechanism from host defences **[4]**. They can also happen from physical or chemical agents, which cannot be broken down, as well as from some kind of genetic susceptibility. Persistence of foreign bodies, continuous chemical exposures, recurrent acute inflammation, or specific pathogens are all crucial reasons for chronic inflammation **[5-6].** Morinda citrifolia is the scientific name of the vegetable widely known as "noni." It is a perennial, fruit-bearing plant that grows up to 6 m tall, which is native to the Southeast Asia. Noni belongs to the family Rubiaceae, the same of the coffee plant, and to the subfamily Rubioideae. It is characterized by large leaves of lanceolate format; its stem is straight and its fruits are sincarpic, oval, and fleshy, with a hard and rough peel in its initial stage of maturation, becoming soft when mature. The noni fruit can measure about 5 to 10 cm in length and 3 to 6 cm in width **[7]**. Moreover, a noni fruit may contain up to 260 seeds. The fruit is also known to have a rather unpleasant odor when it is in an advanced stage of ripening. According to the place of cultivation, noni is also known as Indian mulberry or "nuna" in India, mengkudu in Malaysia, or cheese fruit in Australia. M. citrifolia can grow and develop in different environmental patterns: open rocky or sandy coasts, plains and open meadows, ravines, as a species of colonizing plant in recent flows of lava, or even in humid forests with low luminosity. In addition, the plant reaches maturity in up to 18 months and can produce up to 8 kg of fruits monthly **[8]**. It can also be found in near-bracketed wells in coastal regions, as well as in limestone or concave soils. It can also survive on soils with different levels of acidity. The anti-inflammatory action of Morinda Citrifolia Linn present therapeutic potential in treatment or reducing inflammatory cell infiltration, oxidative stress, pro-inflammatory action of cytokines, COX-2 against inflammatory disorders like UC. Development of effective and economical nonsteroidal anti-inflammatory drugs (NSAIDs) with minimal or no gastrointestinal (GI) side effects is an area of importance in drug discovery pharmaceutical industry. The use of the most frequently recommended drugs of analgesics such as aspirin currently is restricted because of their possible side effects such as severe gastric disorders and other GI side effects. Anti-inflammatory drugs include "biologicals" like anticytokine therapies which block the activity of various kinases and show a significant decrease in host defence toward infections. Due to these side effects and health problems of existing anti-inflammatory therapies, natural anti-inflammatory supplements are becoming more popular and many scientific investigations have been concentrated on this area **[9]**. In recent years, enormous deal of effort has focused on using available experimental techniques to verify natural antioxidant and anti-inflammatory drugs from natural product resources. *Morinda citrifolia* have been used since ancient times in the traditional medicinal systems like, Ayurveda, Siddha, Chinese and many other system of medicines in the treatment of various ailments like, burns, malaria, headache, wounds, cough, cold, liver diseases, hypertension, tuberculosis,skin infections, intestinal worms, diabetes, pain, menstrual disorder, loss of appetite, hernias, urinary tract infection, cancer, cardiovascular diseases, blood pressure, arthritis etc. Seeds and its oil is also used topically on the scalp as insecticide and in the treatment of arthritis. In case of insect stings, flowers are applied topically. The fruits have been used topically in various conditions like, sprains, swellings, wounds and bruises **[10]**.

Material and Methods:

Morinda citrifolia fruit/stem 10g the air-dried powdered was successively extracted with the following solvents of increasing polarity in a soxhlet apparatus. The dried *Morinda citrifolia* stem powder was packed in Soxhlet extractor and extracted with petroleum ether (non polar solvent) for complete extraction, extract filtered and solvent was removed with the help of rotatory evaporator to get petroleum ether extract. The exhausted Morinda *citrifolia* stem powder were dried in air to remove traces of petroleum ether than again packed in soxhlet and extracted with chloroform, filtered and dried to get chloroform extract. The same process was repeated with ethyl acetate and methanol to get ethyl acetate and methanol extracts. After extraction with methanol stem powder were dried and macerated with hot water repeatedly, filter and dried to acquire aqueous extract. Percent yield of the extracts obtained after removing the solvents was calculated. The completion of the extraction was confirmed by evaporating a few drops of extract from the thimble on watch glass to observe that no residue remained after evaporation of the solvent. The consistency, color, appearance of the extracts and their percentage yield were noted.

Antioxidant Study by DPPH Free Radical Scavenging Assay:

The free radical scavenging capacity of extracts of selected plant parts was determined using DPPH assay method. The mechanism involved in the assay is the ability of phyto antioxidant molecules to quench DPPH free radicals (i.e., by providing hydrogen atoms or by electron donation, conceivably via a free radical attack on the DPPH molecule) and convert them to a colourless (i.e.,2,2-diphenyl1-hydrazine, or a substituted analogous hydrazine), resulting in a decrease in absorbance at 516nm. Extract (1 ml) in various concentrations (50, 100,150, 200 & 250 µg/ml) was added to 1ml of 0.1 mM solution of DPPH in methanol. After 30 minutes, absorbance was measured at 517 nm, using a spectrophotometer (SHIMADZU, UV 1800). A 0.1 mM solution of DPPH in methanol was used as blank, whereas ascorbic acid was used as a reference standard. All tests were performed in triplicate. Percent inhibition was calculated using equation,

Percentage inhibition = [(Control ×Test)/ Control] ×100

Then, the concentration of the test compounds required for the 50% reduction in absorbance (IC50) was calculated using the linear regression analysis.

Antioxidant Study by Superoxide Scavenging Assay:

The superoxide scavenging potential of extracts was assessed by the method **[11].**This assay is based on the inhibition of the production of nitroblue tetrazolium formazon of the superoxide ion by the plant extracts and is measured spectrophotometrically at 560nm. **E**xtracts (1 ml) in various concentration (50,100,150,200& 250µg/ml) was added to EDTA (0.2ml), NBT (0.1ml), riboflavin (0.05 ml) and phosphate buffer (2.64 ml). The control tubes were also set up where DMSO was added instead of the extracts. All the tubes were vortexed and the initial optical density was measured at 560 nm in a spectrophotometer. The tubes were illuminated using a fluorescent lamp for 30 minutes. The absorbance was measured again at 560 nm. The difference in absorbance before and after illumination was indicative of superoxide anion scavenging activity. All tests were performed in triplicate. Then, the concentration of the test compounds required for the 50% reduction in absorbance (IC50) was calculated using the linear regression analysis.

Percent inhibition was calculated using equation,

Percentage inhibition = [(Control Test)/ Control] ×100

In Vivo Anti-inflammatory Studies:

The dried extracts of plant were re-dissolved in water using carboxymethyl cellulose (CMC) as suspending agent and this suspension was used for Anti-inflammatory activity. In vitro anti-oxidant studies exhibited the best result for methanolic extract of *Morinda citrifolia* fruits extracts. Hence methanolic extracts were selected for further in vivo Anti-inflammatory studies. Healthy albino rats of either sex, weighing between 180-250g were procured from the disease free animal house of Madhyanchal professional university, Bhopal, M.P. They were housed in standard environmental conditions of temperature, humidity, and light and provided with standard rodent food and water ad libitum. The animals were cared and used in accordance with the CPCSEA guidelines and experimental protocols approved by institutional animal ethics committee **(1698/PO/Re/S/13/CPCSEA).**

Acute Toxicity studies of *Morinda citrifolia* methanol extracts as per OECD guideline:

Acute toxicity studies of methanol extracts of Morinda citrifolia stem and fruits were performed in Swiss Albino female mice (25 to 30 g) dose levels of 50, 300 and 2000 mg/kg as per OECD guide lines. No mortality was observed in rats dosed with the extracts of Morinda citrifolia fruits at dose levels of 50, 300 and 2000 mg/kg (p.o). The treated animals did not demonstrate any significant changes in behavioral pattern and exhibited normal activity. Also there were no clinical signs of tremors, convulsions, exophthalmos, salivation, diarrhea and lethargy. There was no significant difference in the mean body weights between treated groups and control group and the rats exhibited normal body weight gain during the study. No lethal effects or mortality was observed in animals throughout the test period following single oral administration at all selected dose levels of all extracts. The animals were examined for long term toxicity (14 days). The anti-inflammatory activity of suspension of extract of selected plants was evaluated by the carrageenan-induced rat hind paw edema method. The experimental protocol was designed and approval of Institutional Animal Ethics Committee (IAEC) was obtained. The animals were kept in institutional animal house under standard conditions with free access to food and water. Animals Wistar albino rats (150-200g) of either sex were used for experimental study. The animals were housed in cages at 25 ± 2ºC, and relative humidity (50 ± 5%) with 12 h light, and 12 h dark cycle. All the animals were acclimatized to laboratory environment for a week before the experiment. They were provided with free access to food and water ad libitum.

Group I: Untreated & Un-induced
Group II: Untreated
Group III: Diclofenac 10 mg/kg p.o
Group IV (MMCF 200 mg/kg): Methanolic extract of *Morinda citrifolia* fruit
Group V (MMCF 400 mg/kg): Methanolic extract of *Morinda citrifolia* fruit
Group VI (MMCS 200 mg/kg): Methanolic extract of *Morinda citrifolia* stem
Group VII (MMCS 400 mg/kg): Methanolic extract of *Morinda citrifolia* stem

Carrageenan induced hind paw edema:

The initial paw volume was measured using vernier callipers at each individual group of animals. The specific dose of drug diclofenac 10mg/kg or test trial having concentration 200, 400mg/kg via orally administered to animals. Now, 0.1 ml of carrageenan was injected in the right hind leg after 2 h addition of drug. The edema formed in the paw was measured by digital vernier calipers after 3 hours. The degree of swelling provoke was assess by the proportion of the degree of hind paw previous to to after carrageenan treatment. The percentage inhibition was resolute by allowing for edema induced by carrageenan alone was as 100% induction. The statistical as mean ± SEM was performed by one way analyses of variance (ANOVA) with GraphPad Istant3. The $P<0.05$ was considered as statistically significant. 1h prior to the injection of carrageenan. Edema was expressed as the increment in paw thickness due to carrageenan administration. The paw volume was measured using a mercury plethysmometer at the time intervals of 30, 60, 90, 120, 180, 240, 300, 360 minutes after administration of carrageenan. Percent inhibition of edema volume between treated and control group was calculated as follows:

$$\text{Percent inhibition} = \frac{Vc - Vt}{Vc} \times 100$$

Where, Vc and Vt represented mean increase in paw volume in control and treated groups respectively.

Formalin induced hind paw edema:

The initial paw volume was measured using vernier callipers at each individual group of animals. The specific dose of drug diclofenac 10mg/kg or test trial having concentration 100, 200, 400mg/kg via orally administered to animals. Now, 0.1 ml of 2% Formalin was injected in the right hind leg after 2 h addition of drug. The edema formed in the paw was measured by digital vernier calipers after 3 hours. The degree of swelling provoke was assess by the proportion of the degree of hind paw previous to after carrageenan treatment. The percentage inhibition was resolute by allowing for edema induced by carrageenan alone was as 100% induction. The statistical as mean ± SEM was performed by one way analyses of variance (ANOVA) with GraphPad Istant3. The $P<0.05$ was considered as statistically significant **[12]**.

Result And Discussion

***In Vitro* Antioxidant Activity by DPPH Free Radical Scavenging Assay:**

The DPPH radical scavenging potential of plant extracts was concentration dependent. The

potential decrease in the concentration of DPPH radial due to scavenging property for in vitro antioxidant activity of extract in *Morinda citrifolia* (Fruit & Stem) extract showed significant free radical scavenging activity. The petroleum ether, chloroform, ethyl acetate, methanol and water extract of M. citrifolia fruit at five concentrations (50, 100, 150, 200, 250 µg/ml) used for DPPH free radical inhibition and nitric oxide inhibition assay were performed. In this study the methanol extract of M. citrifolia fruit extract at 250 µg/ml concentration displayed, 54.02±3.11 % inhibition for DPPH free radical inhibition and 51.15±2.83 % inhibition of nitric oxide inhibition **(Table 1)**. The petroleum ether, chloroform, ethyl acetate, methanol and water extract of M. citrifolia stem at concentrations (50, 100, 150, 200, 250 µg/ml) used for DPPH free radical inhibition and nitric oxide inhibition assay were performed. In this study the methanol extract of M. citrifolia stem extract at 250 µg/ml concentration displayed, 53.02±4.36 % inhibition for DPPH free radical inhibition and 50.93±1.92 % inhibition of nitric oxide inhibition **(Table 2)**.

In Vivo studies:

In vitro anti-oxidant screenings of extract of M. Citrifolia were performed using various assay methods. Results of in vitro screening illustrate that methanolic extract of M. Citrifolia (Fruit and Stem) revealed highest activity than other extract. The petroleum ether, chloroform, ethyl acetate, methanol and water extract at different concentrations showed considerable in vitro antioxidant activity. Methanol extract of Morida citrifolia fruit and stem showed significant in-vitro antioxidant activity than petroleum ether, chloroform, ethyl acetate, and water extract. Therefore methanol extract of Morinda citrifolia fruit stem (MMCF, MMCS) will selected for futher in-vivo anti-inflammatory activity.

Acute Toxicity Studies:

Plants extracts when orally administered in the dose range of 5-2000 mg/kg mice did not produce any significant changes in the autonomic or behavioural response during the observation period. The body weight was not significantly altered. No mortality was observed up to 14 days of monitoring. So, the extracts were safe for administered up to the dose of 2000 mg/kg.

In vivo Anti-inflammatory Screening.

Carageenan Induced Rat Paw Edema Method:

In carrageenan induced rat paw edema method. The percentage inhibition of rat paw edema of the Methanol extract of M. citrifolia fruit were tabulated in **Table 4** and shown in **Figure 4**. Methanol extract of M. citrifolia fruit showed significant decrease in paw edema volume. The results were compared to the standard Indomethacin. MMCF at the dose of 400 mg/kg showed a maximum inhibition of 74.51 % upto 4 h while the standard showed an inhibition of 78.11%.

Formalin Induced Rat Paw Edema Method:

The percentage inhibition of rat paw edema of the Methanol extract of M. citrifolia fruit were tabulated in **Table 5** and shown in **Figure 5**. Methanol extract of M. citrifolia fruit showed significant decrease in paw edema volume. The results were compared to the standard Indomethacin. MMCF at the dose of 400 mg/kg showed a maximum inhibition of 64.51 % upto 4 h while the standard showed an inhibition of 81.12 %.

Summary And Conclusion:

In conclusion, the current research provides the scientific support for the ethno medicinal use of the selected medicinal plants studied and provides the presence of natural anti-inflammatory activity. The results also substantiate the prospective of medicinal plants as a source of anti-inflammatory lead molecules of pharmaceutical interest. Further works concerning the isolation of active anti-inflammatory compounds and their formulation and evaluation can be perform..

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Table 1: Effect of *Morinda citrifolia fruit* extracts on *in vitro* antioxidant activity by DPPH radical scavenging assay

Plant extract	Concentration (µg/ml)	DPPH free radical inhibition	Nitric oxide
Pet ether extract	50	17.98±2.81	14.18±2.11
	100	27.36±2.94	24.11±2.21
	150	31.64±2.34	29.01±2.02
	200	38.02±2.17	35.99±2.01
	250	44.02±3.11	42.92±2.91
Chloroform extract	50	22.98±2.17	19.18±2.02
	100	31.36±2.24	29.06±2.02
	150	35.64±3.24	33.01±2.94
	200	42.02±3.16	39.03±2.71
	250	49.02±4.15	46.12±3.03
Ethy acetate extract	50	24.98±3.11	21.11±2.91
	100	33.36±2.16	31.01±2.81
	150	37.64±2.34	34.11±2.11
	200	44.02±2.17	42.11±2.81
	250	51.02±3.11	48.12±2.92
Methanol extract	50	27.98±3.11	25.18±2.81
	100	36.36±2.16	34.11±2.72
	150	40.64±3.16	39.13±2.76
	200	47.02±2.17	47.21±2.21
	250	54.02±3.11	51.15±2.83
Water extract	50	25.98±3.11	22.11±2.77
	100	34.36±2.17	31.11±2.87
	150	38.64±3.64	36.21±2.48
	200	45.02±3.27	43.12±2.31
	250	52.02±3.11	49.62±2.82

Values are Mean ± SEM, n=3.

Table 2: Effect of *Morinda citrifolia stem* extracts on *in vitro* antioxidant activity by DPPH radical scavenging assay

Plant extract	Concentration (µg/ml)	DPPH free radical inhibition	Nitric oxide
Pet ether extract	50	15.98±1.11	12.11±1.03
	100	25.36±2.04	22.16±1.91
	150	30.64±2.34	28.11±1.14
	200	36.02±2.97	33.13±1.91
	250	42.02±3.10	39.11±2.87
Chloroform extract	50	20.98±2.110	18.11±1.11
	100	29.36±2.14	26.12±1.04
	150	33.64±2.34	31.01±1.12
	200	40.02±2.17	37.11±1.72
	250	47.02±3.11	44.11±2.11
Ethy acetate extract	50	22.98±1.91	19.23±1.01
	100	31.36±2.04	29.31±1.21
	150	35.64±3.04	34.13±2.14
	200	42.02±3.07	40.14±1.97
	250	49.02±3.91	44.11±2.22
Methanol extract	50	25.98±2.31	23.02±1.43
	100	34.36±2.86	32.02±1.26
	150	38.64±3.45	35.02±2.02
	200	45.02±3.29	44.92±2.03
	250	53.02±4.36	50.93±1.92
Water extract	50	23.98±2.89	20.11±1.02
	100	32.36±2.94	30.03±1.86
	150	39.64±3.54	37.09±1.33
	200	44.02±3.87	41.99±1.23
	250	50.02±3.21	48.11±1.34

Values are Mean ± SEM, n=3.

Table 3: Effect of Ascorbic acid on *in vitro* antioxidant activity by DPPH radical scavenging assay

Standard solution	Concentration (µg/ml)	DPPH free radical inhibition	Nitric oxide
Ascorbic acid	10	35.13±2.23	31.01±1.99
	20	48.29±3.43	45.11±1.76
	30	53.57±2.34	51.43±1.98
	40	61.95±2.58	58.11±1.54
	50	72.68±3.37	67.01±1.12

Table 4: Effect of methanolic extract of *M. Citrifolia (Fruit and Stem)* on carageenan induced rat paw edema method

Treatment (Plant extract)	Dose	1 h		2 h		3 h		4 h	
		EV (ml)	EI (%)	EV (ml)	EI (%)	EV (ml)	EI (%)	EV (ml)	EI (%)
Control		1.79	-	1.63	-	1.59	-	1.51	-
Indomethacin	10 mg/kg	-	48.23	-	57.45	-	69.32*	-	78.11*
MMCF	200 mg/kg	1.23	26.11	1.19	29.03	1.08	37.18	0.91	50.23
	400 mg/kg	1.07	36.18	0.99	53.72	0.88	62.70*	0.79	74.51
MMCS	200 mg/kg	1.29	21.11	1.25	25.36	1.15	31.93	0.96	52.72
	400 mg/kg	1.16	30.32	1.08	37.23	0.99	51.98	0.85	64.51
Values are mean±SEM, (n=5), *P<0.01; EV=Edema Volume, EI=Edema Inhibition									

Table 5: Effect of methanolic extract of *M. Citrifolia (Fruit and Stem)* on formalin induced rat paw edema method

Treatment (Plant extract)	Dose	1 h		2 h		3 h		4 h	
		EV (ml)	EI (%)	EV (ml)	EI (%)	EV (ml)	EI (%)	EV (ml)	EI (%)
Control		2.01	-	1.91	-	1.88	-	1.81	-
Indomethacin	10 mg/kg	-	51.11	-	60.21	-	71.12*	-	81.12*
MMCF	200 mg/kg	1.18	30.71	1.09	38.91	1.01	42.77	0.91	50.23
	400 mg/kg	1.09	38.91	1.01	42.77	0.96	52.72	0.85	64.51
MMCS	200 mg/kg	1.26	24.44	1.23	26.22	1.18	30.71	1.09	38.91
	400 mg/kg	1.21	28.79	1.17	31.32	1.04	45.42	0.88	59.23
Values are mean±SEM, (n=5), *P<0.01; EV=Edema Volume, EI=Edema Inhibition									

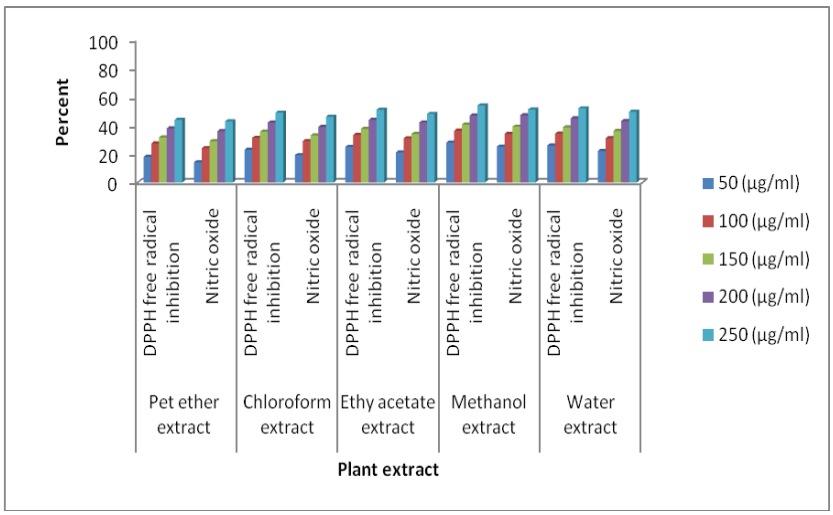

Figure 1: Effect of *Morinda citrifolia fruit* extracts on *in vitro* antioxidant activity by DPPH radical scavenging assay

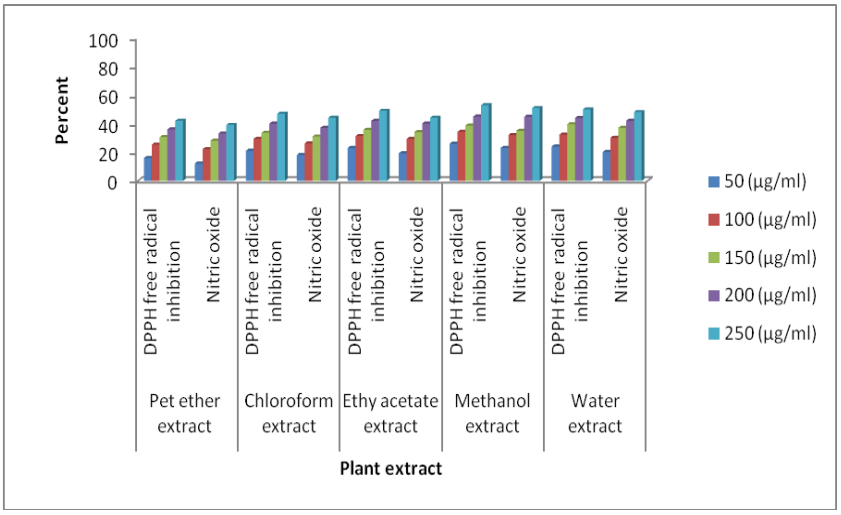

Figure 2: Effect of *Morinda citrifolia stem* extracts on *in vitro* antioxidant activity by DPPH radical scavenging assay

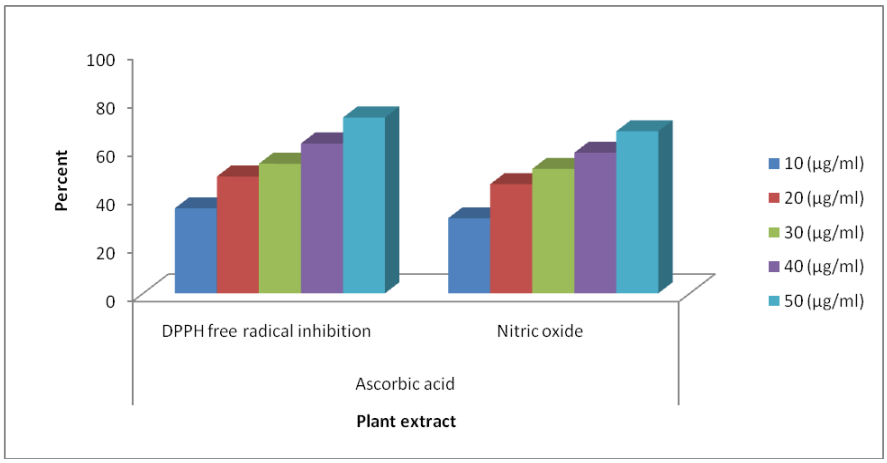

Figure 3: DPPH radical scavenging assay standard (Ascorbic acid)

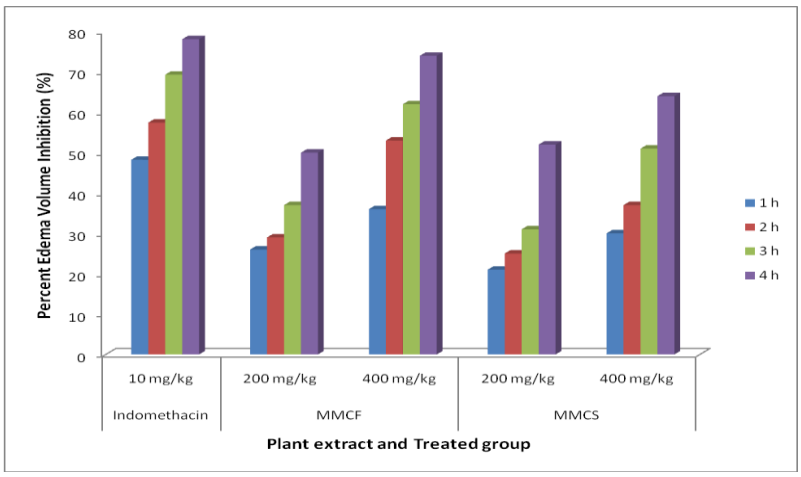

Figure 4: Effect of methanolic extract of *M. Citrifolia (Fruit and Stem)* on carageenan induced rat paw edema method

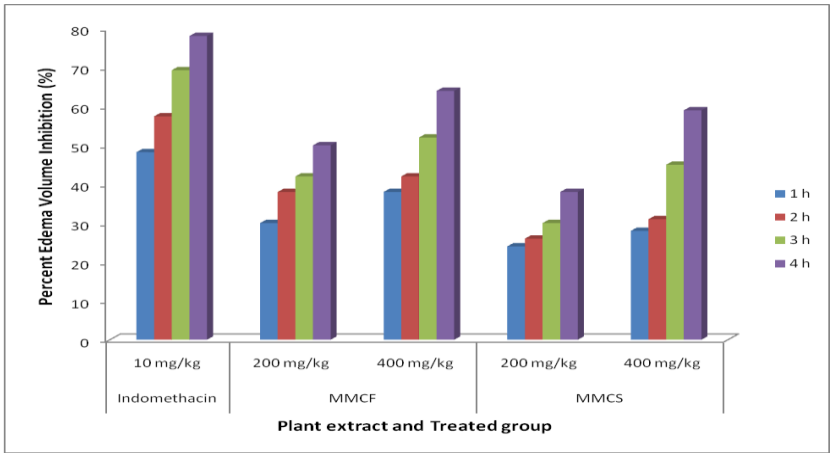

Figure 5: Effect of methanolic extract of *M. Citrifolia (Fruit and Stem)* on formalin induced rat paw edema method