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Anti Pyretic and Analgesic activity of Herbal Formulation: Implications in Managing COVID-19 Fever

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly emergent coronavirus, that was first recognized in Wuhan, China, in December 2019. Genetic sequencing of the virus suggests that it is a beta coronavirus closely linked to the SARS virus. While most people with COVID-19 develop the only mild or uncomplicated illness, approximately 14% develop a severe disease that requires hospitalization and oxygen support, and 5% require admission to an intensive care unit. In severe cases, COVID-19 can be complicated by acute respiratory distress syndrome (ARDS), sepsis and septic shock, multi organ failure, including acute kidney injury and cardiac injury. Reports of the pattern of Covid symptoms suggest that mild fever, cold and cough are the most common symptoms on an average by 5 days after exposure to the virus. Given the current SARS-CoV-2 (COVID-19) pandemic, the availability of reliable information for clinicians and patients is paramount. There have been a number of reports stating that non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids may exacerbate symptoms in COVID-19 patients. There is enough literature to prove that many molecules from plants have shown important therapeutic activity with lesser side effects as compared to conventional medicines. Therefore, the present study is aimed to evaluate Plant extracts of proven antiviral activity, which are described as antipyretics and analgesics in classical Ayurvedic texts for their analgesic & antipyretic effect in laboratory animals. Tab. Febcin formulation was selected.

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INTRODUCTION

Elevated body temperature beyond a normal level is termed as pyrexia. This is conditioned by an increase in thermoregulatory set-point, resulting from the interaction of the CNS (central nervous system) and the immune system. Body's natural defence mechanism against pathogens which highly damage the cells and tissues is nothing but fever (Walter *et al.*, 2016). There is increased formation of triggers like interleukin 1β, α and β, pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α) and this leads to increase in the synthesis of prostaglandin E2 (PGE2) by pro-inflammatory mediators near hypothalamus area and thereby trigger the hypothalamus to elevate the body temperature (Walter *et al.*, 2016). The fever/pyrexia is altered by vasodilation and vasoconstriction of blood vessels by negative feedback mechanism governed by a thermoregulatory system of the body (Walter *et al.*, 2016).

Market of NSAID like Paracetamol, Aspirin, Nimesulide, Indomethacin etc. posses Antipyrectic activity along with some toxicity. The inhibitions of synthesis prostaglandins (PG) by NSAID drugs leads to alleviation of fever and inflammation in the body. The development of novel compounds having antipyretic and anti-inflammatory activities with improved safety profiles remains a clinical need (Walter *et al.*, 2016).

Coming to the current situation of Pandemic of Covid-19, there is an urgent need for this disease management. According to WHO, Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly emergent coronavirus, that was first recognized in Wuhan, China, in December 2019 (Ali *et al.*, 2020). Genetic sequencing results of coronavirus infer a relatably close linkage of SARS virus with beta-coronavirus. While most people with COVID-19 develop the only mild or uncomplicated illness, approximately 14% develop a severe disease that requires hospitalization and oxygen support, and 5% require admission to an intensive care unit. In severe cases, COVID-19 can be complicated by the acute respiratory distress syndrome (ARDS), sepsis and septic shock, multi organ failure, including acute kidney injury and cardiac injury (Li *et al.*, 2020).

Reports of the pattern of Covid symptoms suggest that mild fever, cold and cough are the most common symptoms on an average by 5 days after exposure to the virus. Given the current SARS-CoV-2 (COVID-19) pandemic, the availability of reliable information for clinicians and patients is paramount. There have been a number of reports stating that non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids may exacerbate symptoms in COVID-19 patients. There is enough literature to prove that many molecules from plants have shown important therapeutic activity with lesser side effects as compared to conventional medicines.

Thereby, the study is aimed for evaluation of Plant extracts for Antiviral activity, which are described as antipyretics and analgesics in classical Ayurvedic texts for their analgesic & antipyretic effect in laboratory animals. Tab. Febcin formulation was selected. Contents of Febcin are Musta (Cyperus rotudus), Parpataka (Fumaria parviflora), Duralabha (Fagonia Arabica), Guduchi (Tinospora cordifolia), Shunthi (Gingiber officianalis), Laghupatha (cocculus hirsutus), Yashtimadhu (Glycerrhiza glabra), Usheer (Andropogan muricatum) with phytoconstituents Amentoflavone, Flavonoids, tannins and saponins, Polyphenols, Cordifolioside A, Zingiberene, Hirsutine, Glycerrhizine, Khusimol, zizaene respectively.

Methodology

Model : Baker's yeast induce pyrexia model 20% suspension in 0.9 % NaCl (dose 10mg/ kg)

Dose of paracetamol: 100 mg / kg

Dose of herbal formulation: 500mg / kg

Experimental condition (Och and Suemarub, 2009): Temperature 25 $\pm$ 2 0C; light/dark cycle, 12/12 hr

Procedure

Induction of pyrexia (Och and Suemarub, 2009) Antipyretic activity was measured by slightly modifying the method described by Dewan *et al.* (2014) The rats were divided into four groups of six animals each. Rectal temperature was measured by introducing a 3 cm digital thermometer coated with glycerin (lubricant) into the rectum. Pyrexia (10 ml/kg) was induced by intra-peritoneal injection of 20 % Baker's yeast suspended in 0.9 % saline.

Drug administration

Four hours after yeast injection, the animal groups received orally Herbal formulation (500 mg/kg), paracetamol (reference standard (100 mg/kg) and normal saline water (control), respectively. Body temperature was measured via the rectum hourly from 0 to 4 hr.

Group 1: Normal control receive 0.9% saline water

Group 2: Treated with baker's yeast (Indian Pharmacopoeia, 2014) before treatment with a herbal formulation

Group 3: Treated with baker's yeast (Indian Pharmacopoeia, 2014) before treatment with Paracetamol

Group 4: Receive toxicant baker's yeast (Indian Pharmacopoeia, 2014)

Group 5: Treated with baker's yeast (orally) before treatment with a herbal formulation

Analgesic activity of the herbal formulation

Group 1: Normal control

Group 2: treated with Diclofenac

Group 3: treated with herbal formulation

There was significantly efficacious, dose dependent Antipyretic (Tables 1 and 2) and Analgesic (Tables 3 and 4) likewise the graphical presentation is shown in (Graph 1) & Analgesic (Graph 2) properties noticed after administrating herbal formulation by the IP route with no toxicity. Because of high therapeutic drug safety, Paracetamol is used widely. In case of overdose, most Paracetamol is metabolized to N-acetyl-p-benzoquinoneamine (NAPQI), which

Table 1: Antipyretic data

Test item	Bodyweight (gm)	Initial rectal temperature (°f)	Rectal temperature		Rectal temperature after treatment			
			After 4 hours	After 6 hours	1 hour	2 hours	3 hours	4 hours
Group 1								
1	250	99.5	99.8	99.3	99.2	99.3	99.9	100.0
2	260	100.5	100.1	100.4	100.1	99.9	99.8	100.3
3	240	100.9	101.1	100.8	101.1	101.2	100.4	100.7
4	250	100.2	99.9	100.2	100.4	99.3	99.9	100.2
5	230	100.3	99.8	99.7	100.2	100.7	99.8	100.4
6	250	99.9	100.1	100.4	100.4	100.6	100.2	100.1
Group 2								
1	230	100.2	101.1	102.8	101.9	100.7	99.9	99.8
2	260	100.1	99.8	103.8	103.4	100.3	99.8	100.3
3	240	99.8	100.2	102.4	101.9	100.7	100.1	99.7
4	240	100.4	100.9	103.1	102.7	100.3	99.9	100.6
5	250	100.7	101.4	103.7	102.9	100.4	100.3	100.1
6	250	98.9	100.2	102.2	101.6	99.9	100.0	99.1
Group 3								
1	240	100.8	102.0	103.4	102.6	100.2	100.8	100.6
2	260	100.9	99.5	103.4	102.3	100.3	99.9	100.1
3	220	101.1	102.7	103.3	103.7	100.4	100.7	100.6
4	250	100.7	103.1	103.7	102.9	100.7	100.3	100.4
5	240	100.2	101.7	104.1	103.7	100.9	100.5	100.2
6	250	99.7	101.2	102.9	101.4	99.8	100.1	99.9
Group 4								
1	240	100.1	100.7	101.1	103.4	103.3	102.9	100.5
2	250	100.4	100.6	103.4	103.1	103.6	102.6	101.4
3	230	99.6	100.5	103.8	103.6	103.9	103.4	100.2
4	260	99.2	99.8	102.9	103.1	103.4	103.3	100.1
5	240	100.7	101.4	103.4	103.3	103.9	103.6	101.6
6	250	99.9	100.8	103.1	102.9	103.1	103.4	100.0
Group 5								
1	240	100.0	101.1	101.6	99.7	99.6	99.9	99.8
2	230	99.2	101.2	102.3	100.2	100.6	99.3	99.6
3	250	100.4	100.9	101.6	101.3	100.7	100.4	100.3
4	240	100.6	101.8	102.3	101.6	100.2	100.2	100.5
5	240	100.4	100.9	102.1	101.3	100.9	100.3	100.1
6	260	99.8	100.3	101.9	101.1	100.0	99.9	100.0

Table 2: Antipyretic data

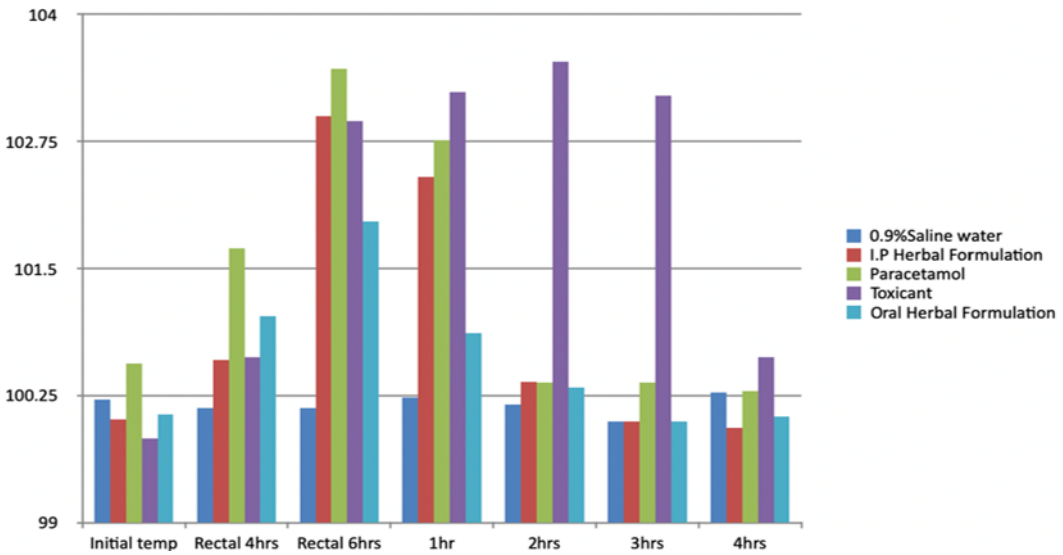
Doses	Initial temp	Rectal 4hrs	Rectal 6hrs	1hr	2hrs	3hrs	4hrs
0.9% Saline water	100.216	100.133	100.133	100.233	100.166	100	100.283
I.P Herbal Formulation	100.016	100.6	103	102.4	100.388	100	99.933
Paracetamol	100.566	101.7	103.466	102.766	100.383	100.383	100.3
Toxicant	99.833	100.633	102.95	103.233	103.533	103.2	100.633
Oral Herbal Formulation	100.066	101.033	101.966	100.866	100.333	100	100.05

Table 3: Analgesic data

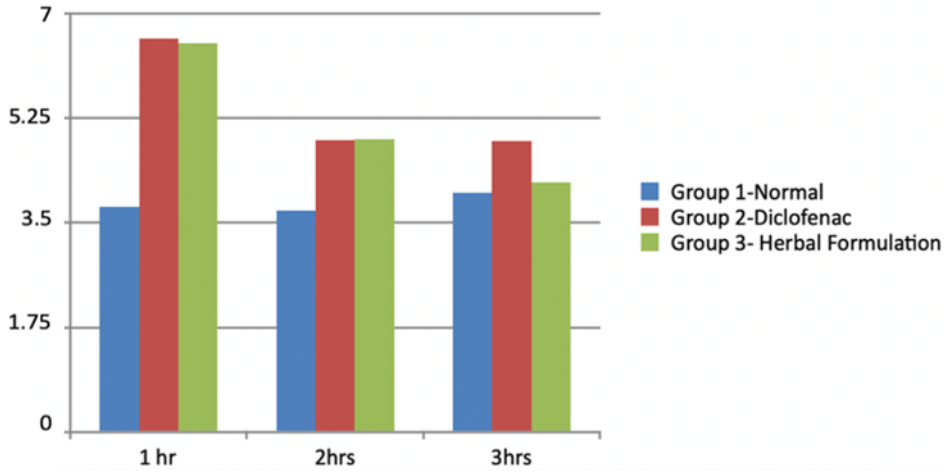
Test item	Body weight in gm	Treatment (time in sec +-0.5)		
		1 hr	2hrs	3hrs
Group 1				
1	240	3.54	4.19	4.02
2	250	3.83	3.49	3.88
3	260	3.98	3.62	4.09
4	240	4.01	4.35	3.76
5	250	3.69	3.41	4.18
6	240	3.56	3.15	4.06
Group 2				
1	260	6.58	5.12	4.51
2	230	6.32	4.98	4.88
3	240	6.84	4.86	4.74
4	240	6.72	5.24	5.04
5	240	6.41	4.91	4.98
6	230	6.63	4.89	5.01
Group 3				
1	230	6.48	4.31	4.43
2	250	6.58	4.89	4.07
3	240	6.73	4.98	4.09
4	240	6.31	5.24	3.98
5	250	6.38	5.30	4.81
6	230	6.49	4.64	3.63

Table 4: Analgesic data

	1 hr	2hrs	3hrs
Group 1-Normal	3.768	3.701	3.998
Group 2-Diclofenac	6.583	4.88	4.86
Group 3- Herbal Formulation	6.495	4.893	4.168



Graph 1: Antipyretic activity



Graph 2: Analgesic activity

is responsible for the severe toxic effects (Mazaleuskaya *et al.*, 2015).

RESULTS AND DISCUSSION

Amentoflavone is the chief phytoconstituent of Cyperus rotundus (Musta). It has been reported to have significant activity against influenza A and B viruses and exhibit moderate anti-herpes simplex virus (HSV)-1 and anti-HSV-2 activities with EC50 values of 17.9 mg/ml (HSV-1) and 48.0 mg/ml (HSV-2).11) It also demonstrated moderate activity against human immunodeficiency virus (HIV)-1 reverse transcriptase (RT), with an IC50 value of 119 mg/ml.17) (Ma *et al.*, 2001). Tinospora cordifolia cordifolioside A, has radioprotective and cytoprotective activity at 120 mg/kg (i.p.) dose and in vitro at 10 mg/ml concentration (Patel *et al.*, 2013). Ginger is well known for preventing motion sickness. Ginger one according to Jeong and Dong (2009) suppresses colon cancer growth.

Yet in another study fresh ginger dose-dependently inhibited HRSV-induced plaque formation in both HEp-2 and A549 cell lines ($p<0.0001$) (Molecule of the Month March, 2018). Fresh ginger dose-dependently inhibited viral attachment ($p<0.0001$) and internalization ($p<0.0001$) (Molecule of the Month March, 2018). Fresh ginger of high concentration could stimulate mucosal cells to secrete IFN-β that possibly contributed to counteracting viral infection (Chang *et al.*, 2013). Thus, ginger has a powerful pharmacodynamics potential through its antioxidant, anti-cancer anti-inflammatory, antimicrobial, anti emetic and hepatoprotective etc. functions according to a study by Balogun (2019). Laghu patha has phytochemical Hirsutin. Hirsutine is also present in *Uncaria rhynchophylla* (TCM).

According to Hishiki *et al.* (2017) and Tietze and Zhou, 1999 Hirsutine was found to exhibit inhibitory effects against the influenza A virus (subtype H3N2), the EC_{50} of Hirsutine was over 10-fold more effective than ribavirin. Thereby, laghupatha is included in this formulation for its effectiveness against broad viral replication and as well for antipyretic action (Hishiki *et al.*, 2017). Glycerrhiza glabra is the most popular drug which is anti viral action against HIV, HCV, cosackie virus and HSV in its property. This effect was evidenced by significantly reduced expression of proinflammatory cytokines, such as nuclear factor–κB, interleukin-1β and interleukin-6 (Wang *et al.*, 2015).

Vetiveria zizanioides is apart from being a powerful antioxidant is also antiviral in action (Chen *et al.*, 2005). Our study at the Haffkine institute has shown it inhibits both the RT and P24 of HIV. The preliminary analysis of Fumaria parviflora revealed flavonoids, glycosides, tannins, saponins, steroids, triterpenoids, phenols, alkaloids and anthraquinones (Kumar and Venkatrathnamma, 2015). Fumaria parviflora possess hepatoprotective, antidiabetic, antiinflammatory, antipyretic, analgesic, prokinetic, laxative, dermatological, antimicrobial, antiparasitic, reproductive, anticholinesterase and smooth muscle relaxant effects (Al-Snafi, 2018).

Another study reveals the antioxidant potential of F. arabica and its protective efficacy against ischemia/reperfusion mediated cell death. F. arabica thus can be considered for further studies for the development of the prophylactic or therapeutic agent for the treatment of ischemic stroke (Satpute and Bhattacharya, 2012). The herbal antioxidants such as polyphenolics can protect the biological systems against the harmful effects of oxidative processes (Satpute and Bhattacharya, 2012). With

all the above information, one can safely use this formulation in the early stage of viral fevers.

CONCLUSION

Results confirm that Febcin, a herbal formulation manufactured by Dr Palep's Medical Research Foundation Pvt. Ltd., when subjected to Antipyretic evaluation using Rat animal models showed significant activities when compared to Paracetamol, a common NSAID used for fever. The constituents are also proven antiviral in the property. Hence, in any viral fever, Febcin can be an excellent alternative to Paracetamol.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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