Case Report

Evaluation of Effect of Sharkara as Anupana on the Bioavailability Enhancer Effect of Haritaki

Vidhate R. Sneha[1*], Deogade S. Meena[1] and Wanjari Anita[2]

[1]Department of Dravyaguna, AIIA New Delhi, India; [2]Department of Rasashastra and Bhaishajyakalpana ,Mahatma Gandhi Ayurved College, Hospital &Research Centre, Salod (H), Wardha, 442001.Datta Meghe Institute of Medical Sciences, Wardha.

Corresponding author: Dr. Sneha Rajendra Vidhate, Assistant professor , Department of Dravyaguna, Mahatma Gandhi AyurvedCollege, Hospital &Research Centre, Salod (H), Datta Meghe Institute of Medical Sciences, Wardha, Tel:8552838670;Email:snehavidhate1@gmail.com

Abstract

Introduction: In the treatment of Ayurveda medicines are prescribed to be taken with various media of intake like warm water, honey, ghee, milk etc. Such substances for Taking medicines are called as Anupana. While treating the diseases anupana plays important role in the treatment. As in Ayurveda there are six different anupana with Haritaki has been mentioned by acharya Bhavamishra. Haritakiprovides the rasayana karma (restorative effect) by cleansing the channels of body. **Objective:** To evaluate the bioavaibality of Haritaki with Sharkara as anupana and to evaluate bioavailability of Haritaki without Sarkara. **Methodology:** Total 60 patient were selected from swastharakshanopd of MGACH and RC. Then Haritaki plant and sharkara will be procured from authentic source. Haritakikwath will be given to patient with and without sharkara after that at a predetermined interval of 0, 30, 60, 90, 120, 180, 240, 300 and 360 min after administration of haritaki, (2 ml) blood will be collected from pre-inserted cannula in the vein and immediately transferred to the EDTA tubes. Finally, the HPLC separation carried out for decoction of dried fruits of terminalia chebula Retz. Along with its bioenhancer effect will be compared with plasma separated from selected healthy volunteers to evaluate the presence of active metabolites responsible for exhibiting antioxidant activities. **Discussion and Conclusion:** Will be drawn on the basis of results found.

Keywords

Bio-avaibality; Haritaki; HPLC; Bioenhancer

Introduction

Ayurveda is supposed to be establishing for last 5000 years in India. It is one of most noted system of medicines in the world.

In healthy condition tridosha, sapta dhatu, and malas balance each other but imbalance causes pathological condition *i.e.* called vyadhi (disease).

In the treatment of Ayurveda medicines are prescribed to be taken with various media of intakes like warm water, honey, ghee, milk etc. Such substances for taking medicines are called as Anupana.

It is also known as vehicle or adjuvant. Vehiculum' is the word which is deriving from Vehicle. The vehicle word derived from Latin word 'meaning that 'carries'.

Adjuvant is also derived from Latin word 'Adjuvans' meaning that 'to add'. For the administration of medicine substance which is used as medium is Anupan or vehicle or adjuvant. [1] While treating the diseases Anupana plays important role in the treatment. Anupana is complimentary substance taken afterwards or along with the principal drugs.

May be it enhances the absorption, action and therapeutic effect of the principal drug. Certain drug may act specifically and effectively when administered with specific Anupana. One herb with different Anupana can acts on different diseases, for e.g. Triphala can give along with warm water in constipation, in diabetes with sugar or turmeric and in splenomegaly with Pippali. Another example is seen in Bhaisajyaratnabalithat Narayanachurna is indicated with different anupana for different diseases like in Udararoga along with takra, Badarakashaya in Gulma, suramadya for vibandhaand usnaambu for Ajirna. [2] The Anupana is claimed to distribute the drug throughout the body within no time. It spreads like oil drop on water *i.e.* spreads in all directly swiftly. The drug will be reaching all part of the

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body by its strength and potency. Anupana facilitate the bioavailability as well as relieve the side effects of medicine. They can also serve as catalytic agent *i.e.* Yogavahi. They help to act direct effect of medicine to the deeper and subtler tissue to the body. [3] The Anupana explicit in 'Anu' means pashchat (later) and 'Pana'means (drinking). It depicts any substance which is taken along with or after food or medicine. On the basis of utility Anupanacan be classified into two types *i.e.* Aharopayogi (advocated with food articles) and Aushadhopayogi(advocated with drugs). It is said to improve the palatability and increase the potency of drug administered in the body and carries essential substance to destination. [4] Anupanashould has properties opposite to the food taken and it should not produce any harmful effect to the body. Individual having predominance of vatadosasnigdhaand usnaanupana, in pitta dosapredominance rukshaandsheetaanupana, in kaphadosapredominance ruksha and usnaanupana has beenadvised. [5] According to AcharyaSharangadhara the Anupanahelps in spreading the drug very fast in body like the oil spreads over the water. [6] There are many Anupanas are described according to roga for e.g. Takra for Grahani, lajaudaka for Chardi,Vidangadikwatha for krimi, Hingu mixed with Ghrita for Shula, Pippali mixes with madhu for puranajwara etc. [7] By this the uniqueness can be considered. This increases the potency of drug used in human by oral route. It is not only mentioned for curing the disease condition but for prevents the health also. Rutuharitaki is the best example of different anupana for rasayana karma for healthy people. For shadarutu six different anupana with Haritaki has been mentioned by acharya Bhavamishra.Haritakiprovides the rasayanakarma (restorative effect) by cleansing the channels of body. [8] The different anupana told for haritaki may have bioenhancer effect. Importantly, any specific drug will exhibit a therapeutic effect when it maintains the minimum effective concentration in systemic circulation. Therefore, the action of specific drug can be enhanced by increasing its bioavailability. That means, increasing the bioavailability, reduces the dosage regimen, reduces the drug toxicity and importantly reduces the regular consumption of expensive drugs. This unique but important concept of Ayurvedawould helpful to retain the effective concentration of drug in systemic circulation in order to increase the bioavailability of active drugs. The concept of bioavailability enhancer (anupana) has not been reported along with any active Ayurveda medicines to confirm their importance while co-administration with active drug. Hence, the objectives of this study is to understand the effectiveness of selected anupana and its interaction with studied active components from species; terminalia chebula Retz. (Haritaki).

Bioavailability

Bioavailability of a drug is outlined because the quantity or share of drug that's absorbed from a given dose type and reaches the circulation following non-vascular administration. [9] The concept of bio enhancer was reported in Ayueveda but no one has attempted it practically to understand their effects of active metabolites from Ayurvedic medicines. Supporting the similar work performed by Bose et al. reported the increasing antiasthamatic effect of Vasakaleave after adding Pippali to it. [10, 11] First time the term bioavailability foil was utilized by Indian Scientists at the Regional work, Jammu (RRL, currently referred to as the Indian Institute of Integrative Medicine), UN agency discovered and scientifically valid chemical irritant because the world's 1st bioavailability foil in 1979. [12] Bioavailability enhancers' drug facilitators, they're the molecules that by themselves don't show typical drug activity and if it's used along, then they enhance the activity of drug molecule in many ways that together with increasing bioavailability of the drug. A 'bio enhancer' is an agent that is capable of accelerating bioavailability and bio efficacy of a selected drug with that it's combined, with none typical pharmacologic activity of its own at the dose used. These (are also|also ar|are) termed as 'absorption enhancers' that are useful excipients enclosed in formulations to boost the absorption of a pharmacologically active drug. [13]

Research Gap

The concept of anupanahas been mentioned in Ayurveda since ancient time. It plays important role in treatment as well as to promote the health. It brings certain changes in a dravya along with it is taken. However, its importance and practical utility does not recognize by modern aspects. Hence there is need to validate the concept of Anupana mentioned in Ayurveda and generate evidences to prove this concept. To achiveRasayana karma one has to consume Haritaki with different Anupana (vehicle) in different Ritu (Season) like saindhavalavana consume with haritaki in Varsha ritu, Sharkara in Sharad ritu, Sunthi in Hemantaritu , Pippali in Shishir ritu, Madhu in vasantritu, Guda in grishmaritu. This is unique concept in Ayurveda so in this study sharakara (Sugar) will be selected as anupana with haritaki in Sharad ritu. There is no any reference found about bioavaibility enhancer effect of haritaki along with Anupana. So the study will be conduct to provide evidence about its effectivity with Sharkara Anupana.

Aim and objectives

Aim

Evaluate the bioavailability enhancer effect of Sharkara as Anupana with Haritaki

Objective

Primary objectives:

To evaluate bioavaibility of Haritaki with sharkara

To evaluate bioavaibility of Haritaki without sharkara

Comparative evaluation of Haritaki with or without Anupana

Secondary objectives:

- To asses and characterize chemical constituents of Drug by using HPLC- Diode Array Detector (DAD) technique)

- To asses and characterize chemical constituent of Drug with Anupana by using HPLC-Diode Array Detector (DAD) technique).
- To evaluate and compare the bioavailability enhancer effect of Drug with Anupana and without Anupana

Research Question

Whether bioavailability of Haritakienhances with Sharkara asanupana?

Source of Study/Study Centre

Swastharakshan O.P.D of Mahatma Gandhi Ayurved College, Hospital and Research Centre, Salod (H.), Wardha (Maharashtra)

Materials

Plant material: Haritaki (Terminalia chebulaRetz.) fruit will be procured from authentic source.
Anupana dravya: Sharkarawill be procured from authentic source.
Healthy volunteers: Will be recruited from swastharakshan O.P.D of Mahatma Gandhi Ayurved College, Hospital and Research Centre, Salod (H.), Wardha (Maharashtra).

Methods

Authentication: Identification and authentication of Haritaki fruit and sharkara will be done from Foundation for Revitalization of local health traditions (FRLHT) Bangalore.

Dose form

Study type: Experimental study.

Place: Healthy volunteers will be recruited from Swastharakshan O.P.D of MGACH & RC. (Screening format attached)

Sample size: The sample size calculation for a bioavailability and bioequivalent study relies on multiple factors like power, intra subject constant of variation, expected mean magnitude relation. Also, as we all know that power and sample size area unit proportionately connected, if we have a tendency to increase the ability the sample size will increase and *vice-versa.* Additional power results in arrange the study with additional sample size. Once we have a tendency to arrange the study with higher sample size we have a tendency to find you defrayment longer and cash. except for time and cash, there area unit different necessary factors like blood, medical waste and participants which will be saved or used additional fittingly, if we are able to arrange bioavailability and bioequivalent studies with cheap sample size. As we have a tendency to all area unit aware that point and cash area unit directly proportional to sample size. According to Bhupathi, et al. power of 85% would be reasonable for a bioavailability study to conduct on healthy volunteers. By considering the values of Lower Bound (LL)=0.80, Upper Bound (UL)=1.25, Alpha=0.05, Geo Mean Ratio (GMR)=0.947, Coefficient of Variation (CV)=0.239 as fixed, the sample size can be calculated as below [Table 1].

The variations of sample size for different Power and GMR values are as below [Table 2].

There area unit clear pointers and suggestions on the sample size and power calculation from health authorities for bio convenience and equivalence studies in healthy volunteers. The recommended power is a minimum of 80th and kind 1 error is five-hitter. In real world things, the clinical trials arrange with over 80^{th}, giving rise to larger sample size. The increased power suggests that a lot of subjects, a lot of wastage of your time and a lot of resources to finish the study, leading to more cash spent.

Unavailability of blood is that the major reason behind death throughout accidents. As per World Bank some wherever somebody wants blood for each a pair of seconds. By recruiting a lot of healthy volunteers, we tend to square measure interference them for a selected time. At constant time we tend to square measure wasting their precious blood that may be wont to save others' lives. Medicine waste may be reduced by recruiting solely needed range of subjects that has vast impact on the atmosphere. So in this study 30 healthy volunteers have been taken considering 85% power and Lower Bound (LL)=0.80, Upper Bound (UL)=1.25, Alpha=0.05, Geo Mean Ratio (GMR) of 0.947.

60 individual divided into two groups.

Group A-30 volunteers will administered Haritaki (Terminalia chebulaRetz.) fruit Kwatha,

Group B-30 volunteers will administered Haritakikwatha along with Sharkara

Sample selection technique: Internet generated random number table.

Study design: Randomized Clinical Trial

Selection of volunteers: Age group from 20 years to 50 years of volunteers, after physical examination and Complete Blood Count (CBC), Blood sugar, LFT, KFT, Lipid profile, Blood pressure with normal values will be selected.

Inclusion criteria

Volunteers of either sex age group between 20 to 40 years, LFT, KFT Lipid profile with normal values, Blood report within normal limits, No history of any major illness and Hypertension, BMI index 18.5 to 24.9

Exclusion criteria

Volunteers with any medication or any acute or chronic disease will be excluded.

History of drug or alcohol abuse, liver, kidney, disorders.

Hypertension, Diabetes, BMI index less than 18.5 and more than 24.9

Groups: Two groups

Safety study: Haritaki (Terminalia chebulaRetz.) Acute toxicity study and sub-Chronic toxicity study of Haritaki conducted on animal suggested that at the dose level (5,000 mg/kg) did not show any signs of toxicity on body weight and internal organ weight and showed normal general behavior, respiratory pattern, cardiovascular signs, motor activities, reflexes, and normal change in skin. [14]

Posology: The Kwatha of fruit will be prepared as per reference mentioned in Sharangadharasamhita. One part of drug with eight part of water will be boiled in low flame and 1/4th will be collected. [15]

Dose: 2 pala (96ml) [16]

Anupana: Sharkara-Half pala (24 gm) [17,18]

Period of intervention: Empty stomach

Assessment criteria:

Objective criteria: Phenolic compounds will be assessed through HPLC method [Table 3].

Volunteers will be randomly divided into two groups. Each group will be consisting of 30 participants. Group A will receive only Haritakifruit kwathain Sharadrutuas a positive control. Group B will receive Haritakifruit kwathawith Sharkarainsharadrutu. The prepared drug will be administered orally.

At a predetermined interval of 0 min, 30 min, 60 min, 90 min, 120 min, 180 min, 240 min, 300 min and 360 min after administration of Haritaki, (2 ml) blood will be collected from pre-inserted cannula in the vein and immediately transferred to the EDTA tubes [Table 4].

Coding of blood sample of Group A and Group B will be mark were 30 patient was selected for each group and the blood will be collected from 30 min to 360 min after every half hour.

HPLC Analysis

The freshly prepared decoction of dried fruits of terminalia chebulaRetz., will be filtered through the 0.45µ nylon filters and will be analyze using HPLC technique. While performing HPLC analysis; different flow rate, sample concentration, column selection and solvent selection and their composition will be tested and evaluated. Furthermore, appropriate HPLC method will be selected which will provide optimum separation of components throughout the analysis. Later, the same chromatographic analysis will be attempted to analyze the blood sample for investigation of any metabolites from decoction of dried fruits of terminalia chebula Retz., which was orally administered to healthy selected volunteers. The freshly collected blood about 2ml from individual volunteer need to be immediately transferred to the EDTA tubes of capacity 5 ml at room temperature. Collecting blood sample in EDTA tubes prevents clotting of blood and separate three distinguished layers after centrifugation at 1200 RPM -1600 RPM for 10-12 min at room temperature. Furthermore, the upper most supernatant liquid was then extracted from centrifuged blood sample and then need to store at 4o C. Under considering HPLC analysis, 1 ml of stored supernatant was mixed with 2 ml of normal saline solution (0.045% NaCl) to make the concentration of 1000 ppm. It was then filtered through the 0.20 µ nylon filters to get clear solution. It was then injected to the HPLC column and eluted with appropriate selection of solvents, their composition, flow rate, wave length and temperature. Finally, the HPLC separation carried out for decoction of dried fruits of terminalia chebula Retz., along with its bio-enhancer was compared with plasma separated from selected healthy volunteers to evaluate the presence of active metabolites responsible for exhibiting antioxidant activities.

Statistical Analysis

One-way ANNOVA with the least significance difference post hoc test for multiple comparisons using SPSS statistics software and p values less than 0.05 will be considered as statistically significant.

Discussion and Result

Discussion and Result will be drawn on the basis of effect of Haritaki along with sharkara as Anupana in Sharad ritu which may be increase bioavailabilty of haritaki. In Ayurveda various medicines prescribe along with drugs as Anupana for better efficacy of drug. In this study we will provide evidence about prescribing drugs with anupana will be augment bioavaibility of drugs for its better efficacy.

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