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Quantitative Systems Pharmacology: Lessons from Fumaric acid and Herbal Remedies

Shyam Sunder Chatterjee[1] and Vikas Kumar[2]*

[1]Stettiner Straße 1, D-76139 Karlsruhe, Germany
[2]National Center for Natural Products Research, School of Pharmacy, University of Mississippi, Oxford, MS 38677, USA

Abstract

Fumaric acid esters, now often used for treatment of psoriasis and multiple sclerosis, have been identified as bioactive constituents of *Fumaria indica* used in traditionally known system of medicine as a liver tonicor for treatments of diverse inflammatory conditions, itches and pain. Observations made during efforts to quantify their roles in therapeutically interesting bioactivity profiles of its extracts strongly suggest that their hydrolysis inside the digestive tract to fumaric acid are involved in their protective effects stress triggered alteration in growth rates and behavior of laboratory rodents. They also reaffirm that repeated daily low oral dose studies is necessary for deciphering the roles of fumaric acid or other food chemicals with bactericidal activities, in quantitative systems phytopharmacology of therapeutically used herbal extracts. Our current knowledge on low dose pharmacology of some such phytochemicals commonly consumed with every day meals, or with herbal remedies, is summarized in this report. Aim of this overview is to point out the necessity of better understanding of quantitative systems pharmacology of food phytochemical not only for more rational medicinal uses of traditionally known herbal remedies, but also for increasing the possibility of success in drug discovery and development ventures. Potential uses of bioassays procedures evolving from efforts to better understand quantitative systems pharmacology of fumarates and other food phytochemicals for such purposes are also suggested.

Keywords: Pharmacology; Herbal Remedies; Inflammatory diseases; Multiple Sclerosis; Phytochemicals; Fumaric Acid

Introduction

Fumaric acid is a metabolic intermediate of citric acid cycle, urea cycle, and amino acid metabolism [1]. This α,β-unsaturated di-carboxylic acid is biosynthesized also in plants via carbon capture mechanisms and processes necessary for their own survival and growth [2,3]. Fumaric acid and its easily hydrolysable conjugates are stored in variable quantities in many plants, and a few reports suggesting fumaric acid and fumarates to be their bioactive constituents have also appeared in recent years [4]. *Fumaria indica* (*Fumaria vaillantii* L.) is one such wildly growing weed often used in traditionally known systems of medicine in India and elsewhere for diverse medicinal purpose [5]. The first report identifying mono-methylfumarate as a potent hepatoprotective constituent of the plant appeared in 1998 [6]. This fumaric acid ester is now considered to be the major circulating metabolite of dimethyl fumarate (Tecfidera® or BG-12), fairly high daily oral doses of which are now used as drugs for treatment of relapsing-remitting multiple sclerosis and psoriasis [7-10]. However, the contents of fumarates in *Fumaria indica* extracts often used in pharmaceutical formulations commercialized in India as liver tonics or as blood purifier are quantitatively much lower than protopine and other alkaloids and phytochemicals encountered in them [11,12]. Therefore, fumarate contents are seldom quantified during analytical standardization of *Fumaria indica* extracts for commercial or investigational purposes. Such neglects of quantitatively minor bioactive constituents during analytical standardization of plant extracts for medicinal or commercial purposes are not very uncommon.

Efforts to define neuro-psychopharmacological activity profiles of some traditionally known Indian medicinal plants led us to identify diverse psychotherapeutic potentials of several of them, including those of *Fumaria indica* [13]. During the course of these efforts, two reports revealing and reaffirming protective potentials of fairly low daily oral dose (20 mg/kg/day) of aqueous *Fumaria indica* extracts against experimental hypochlorhydria had appeared [14,15]. Hypochlorhydria is often caused by bacterial infections and/or metabolic and environmental stress [16,17]. Like in multiple sclerosis, psoriasis and almost all other chronic inflammatory diseases, diverse spectrums of stress triggered psychopathologies are also fairly common in patients suffering from, or at risk to, gastric hypochlorhydria. Since earlier observations in our laboratories had revealed a unique spectrum of psychopharmacological activity profiles of a hydro-alcoholic *Fumaria indica* extract [18], efforts were made to identify and quantify the bioactive constituents of the extract involved in its therapeutically interesting bioactivity profile observed in conventionally known rodent bioassays.

Observations made during these efforts had revealed that although fumaric acid is one of the pharmacologically more potent bioactive metabolite of *Fumaria indica*, stress response suppressing and other therapeutically interesting bioactivities of its extracts are several folds lower than predicted from their contents of fumaric acid and its conjugates only [4]. Aim of this communication is to summarize our current knowledge on systems pharmacology of low dose fumaric acid and other bactericidal food phytochemicals encountered in *Fumaria indica* and all other terrestrial pants, and to suggest a rodent bioassay systems for identifying fumaric acid like ubiquitous plant metabolites for obtaining pharmacologically better standardized herbal extracts, or for obtaining novel therapeutic leads from plants. Necessity of repeated oral dose

***Corresponding author:** Vikas Kumar, National Center for Natural Products Research, School of Pharmacy, University of Mississippi, Oxford, MS 38677, United States of America, Tel: 612-479-9332; E-mail: vkumar@olemiss.edu

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studies with plant extracts and their bioactive constituents for defining their quantitative systems phytopharmacology and for medicinal plants based drug discovery and development ventures, is also pointed out.

Low dose pharmacology of fumaric acid and other food phytochemicals

The very first report suggesting fumaric acid could be used for treatment of psoriasis appeared in 1959. Since then, the numbers of preclinical and clinical reports revealing and reaffirming diverse therapeutic possibilities offered by the acid and its esters have continued to increase considerably [10,19,20]. Although by far a vast majority of such reports deal mainly with di- and mono-methyl esters of the acid, some more recent ones have reaffirmed that fumaric acid itself could also be used for prevention and cure of cancers or as an adjuvant therapy for reducing adverse effect potentials of cytostatic drugs and antibiotics [21,22]. It is now well recognized that like numerous other food phytochemicals, fumaric acid is also a bactericidal and cellular stress response modulating hermetic plant metabolite [23,24]. Therefore, it can be expected that some of its modulating effects on the physiological functions regulating stress responses should be qualitative similar or analogous, to those of other phytochemicals and that appropriate combinations of fumaric acid with other drugs and food phytochemicals could be used for prevention and/or cure of stress triggered diseases and their syndromes.

Nutritional and other researchers have since long well recognized that biological interactions between food phytochemicals could be involved in the protective effects of vegetables and fruits against cancer, diabetes and other chronic inflammatory and degenerative diseases suggested by numerous epidemiological studies [25-28]. Quantitatively though, the contents of most, if not all, phytochemical commonly consumed with meals or herbal remedies are fairly low. Therefore, it is apparent that proper understanding of their low dose pharmacology and their combination effects is essential for deciphering the complexities involved in their health benefits or therapeutic potentials. Consequently, efforts were made to identify bioassays that could be used for such purposes. Some of the very first experiments conducted during such efforts were designed to compare the anti-inflammatory and analgesic like activities of pure fumaric acid with those of its mono- and di-methyl esters in conventionally known rodent models often used for drug discovery purposes [29]. Results of those experiments revealed that like the two esters tested, low daily oral doses of fumaric acid also possess anti-inflammatory and centrally acting analgesics like activities, and that their effectiveness in all rodent models used increases with increasing numbers of treatment days. Estimated daily effective dose ranges of fumaric acid and esters tested after their once daily treatments for 7 consecutive days in all such models were between 2-5 mg/kg/day in laboratory rodents.

These observations reaffirm that like many drugs and plant extracts [30,31], bioactivity profiles of fumarates quantified after their single oral doses, or in cellular and other *in vitro* models, are not very definitive predictors their therapeutic potentials or effectiveness often observed after their repeated daily oral doses. That such is indeed the case is in agreement with several other recently reported observations reaffirming stress response suppressing, anti-ulcer, and antidepressant and anxiolytic like activities of daily oral 10 mg/kg doses of fumaric acid and its mono-methyl ester [4,32,33]. These observations, taken together with available information on oral bioavailability and membrane permeability of fumaric acid and its esters [34,35], strongly suggest that hydrolysis of dimethyl fumarate inside the digestive tract to fumaric acid and its mono-methyl ester also contribute to systems pharmacology of the medicinally used esters of the acid and that blood levels of fumaric acid and its esters observed after their oral doses are not very reliable predictors of their durations of actions or therapeutic potentials. Moreover, since cell permeability of fumaric acid is almost negligible, it can be inferred also that fumaric acid is a non-systemic drug like molecule [36,37] and that its modulatory effects on the biological functions of extracellular space (and/or receptors) inside the gastro-intestinal tract are involved in its modes of action.

Fumaric acid has since long been used as food preservative and farm animal growth promoter, there is now considerable experimental evidences that like diverse other organic acids used as gastric acidifiers, such uses of fumaric acid is also due to its ability to alter intra-gastric hydrogen ion homeostasis and gut microbial ecology [38,39]. Pivotal role of gut microbiota in regulating stress induced gastric damages and health status is now well recognized as well [40,41]. Therefore, it seems reasonable to assume that modulation of these functions of the digestive tract are also involved in the low dose anti-stress and other therapeutically interesting bioactivities of the fumaric acid. Although it has since long been well recognized that fumaric acid is biosynthesized and released by microbiota as well, the role of such intra-gastric processes in regulating allostatic load, energy homeostasis, and human health still remain to be better understood. Therefore, efforts were made to verify whether or not the bioassay procedures evolving from our efforts to define low dose pharmacology of other bactericidal organic acids and phytochemicals [42-45] could also be used for better understanding of such intra-gastric physiological processes.

Using one such bioassay, it has recently been reaffirmed that 5 mg/kg/day oral doses of fumaric acid as well its mono-methyl ester are high enough not only for antagonizing stress triggered alterations in body weight and core temperature, but also in modulating depressive or anxiety states of mice occasionally subjected to fairly short duration of (<1 min) unpredictable foot shock stress [33]. In this study, the activity profiles of single and repeated daily oral doses of fumaric acid and mono-methyl fumarate were compared with those of quercetin (a plant phenolic encountered in many medicinal and food plants) and triethylene glycol, i.e., a bactericidal agent often used as air purifier. Dose dependent (between 1.25 and 5 mg/kg/day) protective effects of mono-methyl fumarate against more severe and chronic foot shock stress induced gastric ulcers and other metabolic and physiological alterations have also been observed in another study [32]. These observations add experimental evidences in support of the hypothesis proposed in 1959 by German chemists and other researchers that alteration in fumaric acid homeostasis, and/or fumaric acid deficiency, could be a risk factor of inflammatory psoriatic diseases [46,47]. Therefore, it seems reasonable to suggest that the bioassay systems described in the recently study [33] could be a feasible starting point for better understanding the role of intra-gastric fumarate and hydrogen ion homeostasis in regulating stress responses and systemic inflammatory processes.

Some other phytochemicals and drugs tested to date for their stress response modulating or adaptogenic activities in analogous bioassays have already been published (Table 1) and these assays are progressively emerging. Diversity of structures of the already tested phytochemicals strongly suggest that their observed anti-stress activity is most probably due to the presence of acidic protons in their structures, or due to their intra-gastric metabolism to acidic metabolites. These observations strongly suggest also that depending on their physicochemical properties and membrane permeability, pharmacological targets of structurally diverse phytochemicals and their intra-gastric metabolites can reside both inside and outside the cellular space of the digestive

Phytochemicals	Protective effects against stress-triggered alterations in body weight and/or temperature after repeated oral doses	References
Table 1A: Phytochemicals		
3- and 4-hydroxybenzoic acids	+	[42,45]
Andrographolide	+	[50,79]
Ascorbic acid	+	[44]
Curcumin and curcuminoids	+	[76-78]
Fumaric acid and Methyl-fumarates	+	[4,6,9,29,49]
Hyperforin	(+)	[67,117]
Lactic acid	+	[43]
Nicotinic acid	+	[45,42]
Phloroglucinol and its tri-methyl ether	+	[118]
Piperlongumine	+	[48,100]
Quercetin	+	[33]
Salicylic acid	+	[45,42]
Sinapic acid	+	[119]
Triethylene glycol	+	[33]
Table 1B: Drugs		
Aspirin	+	[45,42]
Diazepam	(+)	[120]
Doxycycline	(+)	[48,100]
Fluoxetine	(+)	[121]
Imipramine	(+)	[122,123]
Metformin	+	[76-78]

+: Low dose effects observed; (+): Minimally effective doses were not estimated

Table 1: Some food and other phytochemicals and drugs tested for their stress response suppressing activities.

tract. Except for nicotinic acid [42] and piperlongumine [48], fumaric acid and its esters are some of the orally most potent stress response modulators with anti-inflammatory and analgesic activities tested to date in our laboratories or elsewhere. Although, after their repeated daily oral doses, all of them were very effective in antagonizing longer lasting and gradually progressing losses in body weights and slight increases in temperature in animals occasionally subjected to short durations (<1 min) of unpredictable foot shock stress, their bioactivity profiles after their higher daily doses were seldom identical. Their maximally possible protective daily oral doses against stress triggered alterations in growth rates and body temperatures were always observed after their lowest daily doses tested (between <1 to 20 mg/kg/day). These observations add experimental evidence to our working hypothesis that modulation of intra-gastric digestive processes regulating body weight and temperature are involved in their low dose pharmacology, and that their ability to alter the physiological functions of gut microbiota regulating intra-gastric hydrogen ion homeostasis [29,48-50], are also involved in their anti-stress, or adaptogenic, and other therapeutically interesting bioactivities.

Detailed discussion on possible pharmacological sites and biological processes involved in modes of action of fumaric and other organic acids and their precursors are beyond the scope of this report. It must be mentioned though, several so called orphan receptors regulating glucose and lipid metabolism have already been identified as receptors of structurally and functionally diverse organic acids and their precursors, and their presence and abundance inside the digestive tract has often been reported as well [51,52]. Since acclimatization-induced stress influence also host metabolic processes [53] and many organic acids and their metabolic precursors are fairly potent stress response modifier, they seem to be promising pharmacological tools for deciphering the roles of such receptors in regulating stress triggered alterations in growth rates and thermoregulation. Fumaric acid is one of the more potent stress responses modulating organic acids that can also suppresses unpredictable foot shock stress triggered hyperthermic responses even after its single fairly low oral dose [4,33]. Therefore, this acid seems to be particularly well suited for better understanding of the roles of intra-gastric acidic milieu and other biological processes involved in regulating acute as well as longer lasting effects of stress triggered alterations in thermoregulatory metabolic processes.

There is now considerable evidence that many organic acids and the so called "endocannabinoid system" are involved in modulating allostatic load or stress responses [54] and that modulation of the functions of this system is also involved in the modes of actions of many acidic and other food phytochemicals [55]. Although the endocannabinoid system has also been well recognized as a promising therapeutic target by drug hunters [56,57], the question whether to enhance or reduce the biological functions of the system for obtaining health benefits still remain open or speculative [58,59]. Efforts to quantify the dose and time dependant effects of fumaric acid like stress response modulating agents and their combinations on intra-gastric endocannabinoid system could be useful not only for better understanding of their roles in modes of actions of herbal extracts, but also for more precisely answering such questions. Potential uses of the experimental strategy currently used in our research group for better understanding of low dose systems pharmacology of fumarates and other food phytochemicals and herbal extracts for such purposes are discussed in the following.

Bioassays for quantitative systems pharmacology

It cannot be overemphasized that proper knowledge on quantitative systems pharmacology is a prerequisite for more rational and evidence based medicinal uses of herbal extracts, or for obtaining therapeutic leads from them [60-63]. For such purposes, it is essential to have better quantitative knowledge on the contents of most, if not all, bioactive constituted of a given extract. Since all such extracts contains hundreds of known or unknown substances, it is almost impossible, or impracticable, to analytically quantify them all. Therefore, most such extracts currently commercialized, or used for experimental purposes, are analytically standardized on their contents of a few of them and their chromatographic fingerprints [64]. However, many time-consuming and expensive analytical technologies and facilities necessary for such purposes are often not available or accessible to many herbal research groups, like ours, interested in better understanding of systems phytopharmacology of traditionally known medicinal plants, or for obtaining drug leads from them.

Therefore, attempts were made to identify and validated bioassays that could be used for pharmacological standardization of herbal extract in many laboratories for increasing the reproducibility of preclinical observation of herbal extracts necessary for obtaining sustainable and more reliable health benefits from phyto-pharmaceuticals and nutraceuticals. Hereupon due attention was paid to the fact that traditionally known medicinal uses of herbal remedies are based on the observations and experiences of numerous medical practitioners and consumers made after oral consumption of mixtures of plant derived products (containing relatively small amounts of structurally and functionally diverse phytochemicals) for more than a day or two. Diverse combinations of known or as yet unknown food phytochemicals are encountered not only in crude extracts of edible plant currently often used as tonics or rejuvenators in Ayurvedic system of medicine [13,65-67] and also in almost all traditionally known medicinal plants often

pharmacologically classified as herbal adaptogens [68-72]. Despite their widespread and popular medicinal uses, as yet very little concentrated efforts have been made to better define their quantitative medicinal phytochemistry and systems pharmacology. One consequence of the situation is that European and other health authorities still continue to be reluctant to accept adaptogenic phytochemicals and herbal remedies as approvable or recommendable drugs and therapeutic options [73]. Curcumin and turmeric extracts are just some examples of pre-clinically and clinically well scrutinized food phytochemical and herbal extracts still controversially discussed by modern drug hunters a potential drug leads or therapeutic alternatives [74,75].

Preclinical and clinical information now available on curcuminoids and turmeric extracts strongly suggest that they could be effective, safe, and economically more affordable therapeutic options for prevention and cure of metabolic disorders associated mental health problems and that their modes of actions are quite analogous to those of the anti-diabetic drug metformin [65,76]. More recent observations in our research groups [77,78] reaffirm such inferences and suggest that appropriate uses of the foot shock paradigm and repeated daily low oral dose studies could be helpful in resolving such controversial discussions depriving us from more rational uses of experience based knowledge on traditionally known herbal remedies for prevention and cure of diseases and their syndromes. The very first observations triggering our interest in exploring the foot shock stress paradigm for preclinical studies necessary for quantifying systemic effects of food phytochemicals and plant extracts were made during our efforts to compare bioactivity profiles of fumaric acid and its esters with those of a *Fumaria indica* extract [4]. In those experiments, effectiveness of stress response modulating and other bioactivities of the extract tested were ca. 10 folds lower than those predictable from its analytically quantified fumarate contents only. Using repeated daily oral doses of test agents, several such "negative" interactions between bioactive phytochemicals and other components of plant extracts have often been made in our laboratories (see for examples [50,77,79]) and elsewhere using repeated daily oral doses of test agents.

On the other hand, there is also no dearth of reports suggesting or revealing synergistic "positive" interactions between plant derived products, antibiotics and other drugs also [80-82]. However, more often than not, most such reports deal either with diverse theoretical possibilities, or with observation made *in vitro* and in animal experiments after singleoral doses and that too dealing mainly with acute or short term effects of test agents. They also often neglect several now well recognized facts summarized in Table 2. The fact that *in vivo* studies using oral doses has to be used for translating currently available preclinical knowledge on phytopharmacology and medicinal phytochemistry of plant derived products for health benefits, or for drug discovery purposes, has often been pointed out during more recent years [83-85]. Some systems phytopharmacology lessons (relevant for discovering and developing drugs from traditional knowledge and plant metabolites) learned from the observed low dose effects of fumaric acid, curcumin, and other drugs, antibiotics, and plant extracts after their single and repeated doses are summarized in

S. No.	Inferences
1	Various combinations of so called “food phytochemicals” [124] are biosynthesized and stored in all terrestrial plants and can also contribute to their medicinally interesting bioactivity profiles of their extracts.
2	Plants biosynthesize and store phytochemicals not only for their nutritional demands, but also for protecting themselves from predators and stress [125].
3	Many phytochemicals altering brain functions do so by regulating the physiological functions of digestive system and autonomic nervous system [126].
4	Gut microbial ecology plays a crucial role in dictating gut feelings and metabolic status of all animals necessitating plant derived food for survival and health maintenance [126-131].
5	Observable acute dose effects of drugs and other bioactive substances are not very predictive of their therapeutic potentials or health effects, or pharmacological activity profiles, and could as well be opposite of those observed after their repeated doses [30,132,133].
6	Modulation of stress responses by phytochemicals and drugs and their combinations is involved in their regulatory effects on metabolic processes and mental functions dictating health status of all living organisms including humans [24,134].
7	Pre-existing allostatic load of a given individual dictates the effects of drugs or of any therapeutic measure, on a given day and age of his life depends on his prior physical and mental health status formed by his eating habits and ability to adapt and react against diverse environmental challenges and mental stress [135,136].

Table 2: Some facts well recognized by modern biologists, physiologists and pharmacologists, but often neglected by drug designers and others interested in better understanding of medicinal phytochemistry and phytopharmacology of herbal remedies.

S. No.	Inferences
1.	Like vitamins and other essential micronutrients, diverse combinations of phytochemicals, edible or not, regulate stress resistance or allostatic load, and thus protect them from adverse effects of metabolic and environmental stress necessary for survival and prolonging healthy life or for obtaining therapeutic success with all drugs and other treatment modalities.
2.	Except alkaloids and a few other phytochemicals well known to be potentially toxic, a vast majority of extractable secondary plant metabolites with molecular weights below 500 are well tolerated after their reasonable oral doses and their health effects depend on their combinations consumed with food and/or herbal remedies.
3.	Pharmacological relevant daily oral doses of structurally and functionally diverse phytochemicals can afford protection against environmental stimuli triggered altered biological responses even several days after their last oral doses.
4.	Such slowly evolving and longer lasting protective effects of most non-toxic or low daily oral doses of toxic phytochemicals do not solely depend on their blood levels observed after their single or repeated daily oral doses.
5.	Better understanding of quantitative systems phytopharmacology of plant extracts is possible only when due attention is being paid to preconditioning, signaling, transmitting, and rebound effects of phytochemicals and their combinations.
6.	For such purposes, repeated low dose studies using oral route of administration has to be used, and due attention has to be paid to the possibility that numerous bioactive substances, including drugs and numerous food phytochemicals could also modulate cognitive functions of the central as well as peripheral nervous system regulating energy homeostasis.
7.	Mixtures of phytochemicals in an extract obtained from a given part of a plant depend not only on the genetic background of the plant, but also on environmental factors and harvesting, processing and extraction procedures used for obtaining it.

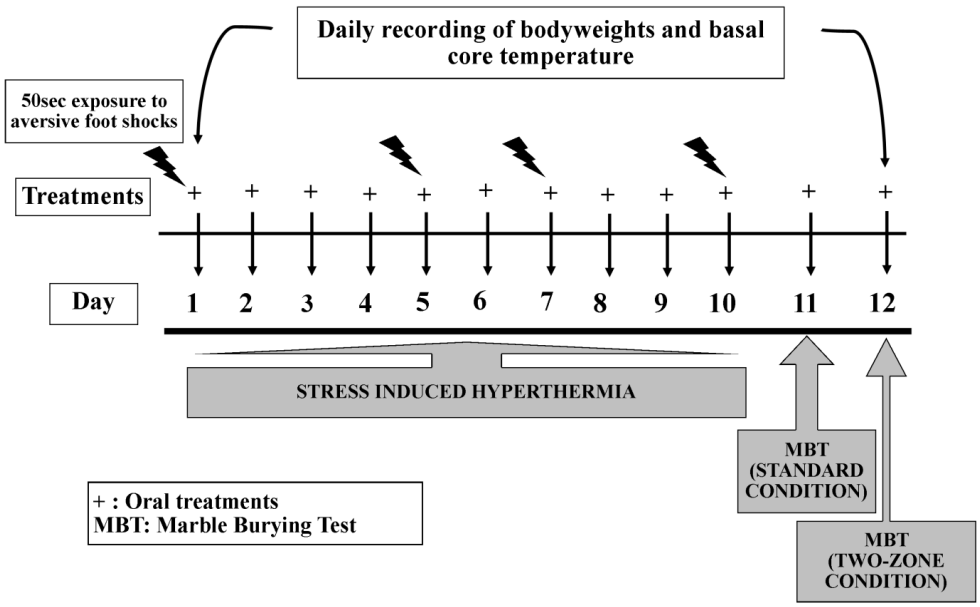
Table 3: Some inference from preclinical observations made during our efforts to identify therapeutic leads from *Fumaria indica* and other adaptogenic plants used in traditionally known Indian system of medicine.

Table 3. Consistent neglect of these facts by phyto-pharmacologists and other drug discoverers have not only hampered more rapid progress towards integrative medicine, but also are some of the major reasons behind numerous controversial discussion and misinterpretations of traditionally known medicinal values of numerous plant derived products, including those of numerous analytically well standardized phytopharmaceuticals and nutraceuticals [74,86-91].

Such controversial discussions arise not only from the complexities of medicinal phytochemistry, but also from many as yet unsolved problems concerning reproducibility and predictive validity of preclinical models and *in vivo* bioassays [92,93]. Drug discoverers and developers have since long well recognizedthat due attention has to be paid to role of stress (induced by handling, treatment regimen and housing and experimental conditions, etc. necessary for conducting experiments) responses of experimental animals for increasing the predictive validity and reproducibility of pharmacological observations [94]. The possibility that traditionally known medicinal plants posses stress response regulating or adaptogenic, properties have also been known to pharmacologists since more than seven decades [95,96] and the usefulness of the foot shock paradigm for better understanding stress response modulating potentials of drugs and other therapeutic measures has been well recognized as well [97]. However, experimental pharmacologists and drug discoverers often neglect the facts that depending on the nature and intensity of stress or on the doses of dosing regimen of drugs used, their homeostatic and behavioral responses could have very long lasting adverse or beneficial effects [98,99].

Results of a more recently reported study [100], using the foot shock stress induced hyperthermia test, strongly suggest that slowly evolving and longer lasting physiological response of repeated exposures to very short duration of foot shock stress can also be prevented by prior repeated daily oral administrations of antibiotics, and bactericidal phytochemicals and plant extracts. In that study, only 5 mg/kg daily oral doses of piperlongumine or a *Piper longum* extract for 10 consecutive days not only antagonized stress triggered alterations in body weight and temperature, but also stress triggered exaggerated depressive state of animals quantified 11 days after the last dose of the test agents. These observations reaffirm not only the reproducibility of the foot shock stress paradigm often used in our studies for assessing the pharmacologically and toxicologically interesting dose ranges of test agents, but also for evaluating the durations of actions of their protective effects against repeated exposures to unpredictable stress triggered alterations in physiological thermoregulatory, metabolic and behavioral processes.

These observations encouraged us to develop and pharmacologically validate a simplified test procedure (using foot shock stress induced hyperthermia test) that could be used in many laboratories for obtaining therapeutic leads from plants and other natural products, or for better understanding the role of food phytochemicals and their combinations commonly consumed with everyday meals in dictating human health. One such test procedure now often used for such purposes in our research groups is graphically summarized in Figure 1 and the results of some confirmatory experiments using this test procedure has also been published [33,101]. Observations made during these efforts, reaffirm that this test procedure is well suited for estimating the pharmacologically and toxicologically relevant oral dose ranges and treatment regimen of test agents and drugs with potentials to alter the physiological functions of the so called "microbiota-gut-brain-axis" regulating metabolic processes. It cannot be overemphasized that gut microbial ecology plays a pivotal role in regulating human health and that appropriate animal models are urgently needed not only for drug discovery and development purposes, but also for better understanding of the physiological adaptive processes regulating physical and mental health [102-106].



Adapted from: [33,101]

Figure 1: Summary of an experimental procedure potentially useful for better understanding of quantitative systems pharmacology of herbal remedies, nutraceuticals, drugs and drug leads.

Concluding Remarks

Despite extensive efforts and considerable progress made towards better understanding the role of gut microbial ecology in dictating physical and mental health, our current knowledge on the biological processes and mechanisms involved in regulating the physiological functions of the microbiota-gut-brain axis still remain poorly defined [107,108]. It is now well recognized though, that microbiota rely heavily on small molecules to interact with their environment [109] and that those residing inside the digestive tract dictate oral bioavailability (as judged by circulating blood levels after their orally intake) and systems pharmacology of all drugs and xenobiotics [110]. Although oral bioavailability of many phytochemicals and their intra-gastric metabolites are often negligible or very low, the numbers of reports revealing and reaffirming, broad spectrums of therapeutically interesting bioactivity profiles and health benefits of numerous of them have consistently increased during more recent decades. Amongst ~20,000 food phytochemicals currently listed in modern data bases [111], salicylic acid and curcumin are pharmacologically and toxicologically the more extensively scrutinized ones, and there is no dearth of reports reaffirming their therapeutic potentials for prevention and cure of chronic inflammatory disorders associated physical and mental health problems [112,113].

Central hypersensitivity to pain, abnormal changes in body weight and temperature, and loss of appetite are cardinal symptoms of almost all such chronic inflammatory diseases [29,114,115]. Therefore, efforts were also made in our research groups to identify drug leads and phytopharmaceuticals or nutraceuticals that could be further developed for prevention and cure of such co-morbidities. Observations made to date in our research groups with mono-hydroxy benzoic acids, curcuminoids, and piperlongumine strongly suggest that they are promising therapeutic leads for such purposes, and that their appropriate combinations with the anti-diabetic drug metformin could be used for combating such co-morbidities in patients suffering from diabetes and other metabolic disorders [45,48,76,78,116]. Therefore, efforts are now being made in our research groups to identify biomarkers that could be used for clinically verifying predictive validity of the preclinical observations made with them in our laboratories and elsewhere. For obtaining blood, saliva, urine and other biological samples necessary for such purposes, animals treated with the test agents and their combinations and subjects to the bioassay procedure summarized in Figure 1 are now used in our laboratories. Several as yet unpublished observations made during such efforts strongly suggest that metabolic functions regulated by peroxygenase and cholinesterase are involved in the modes of actions of many phytochemicals.

In any case, it remains certain that bioassays based on appropriate uses of foot shock stress paradigm and repeated daily oral doses of test agents is promising starting point for better understanding of medicinal phytochemistry and pharmacology of plant extracts, or for obtaining functionally novel and economically more affordable therapeutic leads from them. During efforts necessary for such purposes, or for better understanding of quantitative systems pharmacology of drugs and drug leads (plant derived or not), due attention has to be paid to the slowly evolving but longer lasting preconditioning like effects of numerous food phytochemicals (and their combinations commonly consumed with every day meals) on digestive processes and gut microbiota regulating our physical and mental health. Fumaric and numerous other organic acids and structurally simple phenolics are ultimate or penultimate (and often analytically undetectable, or transient) metabolites of numerous substances consumed orally with drugs and food. Therefore, proper understanding of their modulating effects on the physiological functions of the microbiota-gut-brain axis seems to be an essential prerequisite not only for discovering and developing drugs potentially useful for prevention or cure of diseases, illnesses and their syndromes, but also for better understanding of quantitative systems pharmacology of any orally consumed drug, phytopharmaceuticals or nutraceuticals. Knowledge and knowhow evolving from such efforts will certainly be useful for increasing the possibility of success in efforts to discover and develop drugs from traditionally known medicinal plants and their secondary metabolites.

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Commercial Interests

Both of us never had any commercial interests in any of the phytochemicals or plant extracts mentioned in this report. The experimental works conducted by the students were financially supported by diverse governmental non-profit organizations in India.

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