

RESEARCH ARTICLE

## The Use of Natural Products as an Adjunct in the Treatment of Hypertension: A Case Study with Mango-Ginger Tea

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**Received:** December 23, 2022      **Published:** January 05, 2023

**Citation:** Orien LT. The Use of Natural Products as an Adjunct in the Treatment of Hypertension: A Case Study with Mango-Ginger Tea. Int J Complement Intern Med. 2023;3(1):85–91. DOI: 10.58349/IJCIM.1.3.2022.00113

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### Abstract

A mango leaf-ginger combination was added to the pharmacologic regimen to improve the clinical management of chronic mid-grade hypertension (HTN) in an NIDDM patient with effective glycemic control. Measures of systolic and diastolic blood pressure (SBP and DBP respectively) were obtained for the 4 weeks of control monitoring when taking a multidrug pharmacologic treatment consisting of metoprolol succinate, losartan potassium, and amlodipine (MLA regimen) for 6 months or more, followed by 4 weeks of a mango-leaf+ginger tea (MGT) combination. Measures of systolic (SBP) and diastolic BP (DBP) were obtained 6-12 hours after the multidrug regimen and resulted in a 13% decrease in both SBP and DBP after one week, a 17% reduction in both parameters after two weeks, and a 30% reduction at weeks 3 and 4 of the MGT trial. These results indicate that the addition of the MGT natural product regimen when added to the MLA treatment was contributing to a normalization of BP and an amelioration of HTN when the MLA regimen alone was incompletely effective due to multi-drug resistance or other factors.

**Keywords:** Hypertension, Diabetes, Allopathic drugs, Natural Products, Complementary and Alternative Therapies

### Introduction

The clinical manifestations of hypertension are often present without exhibiting overt symptoms, particularly during the early stages of the disorder, but the pathophysiologic sequela commence well before overt

symptoms may become evident, resulting in the often referenced moniker as a ‘silent killer’ of those affected.<sup>1</sup> The prevalence of hypertension ranks among one of the most challenging disorders in global public health concerns where it impacts the health of approximately one quarter of the adult population, despite the ready availability of

numerous largely effective pharmacotherapeutic agents in Westernized societies.<sup>2</sup> However, not all patients are managed adequately when taking one or more prescription agents, and secondly, not all patients may enjoy ready accessibility to the usual assortment of antihypertensive agents due to a variety of economic, geopolitical, and other factors. For many, the use of Complementary and Alternative Medicines (CAM) including various natural remedies to treat the common disorders and illnesses that may afflict humankind become the first and sometimes the only available line of therapeutic agents for a family member, loved one or member of their community. The practice of Traditional Medicine, which utilizes a wide variety of time proven natural remedies is growing in popularity and preference in Western Societies.<sup>3</sup> Natural therapies have been used successfully in Traditional Chinese Medicine (TCM) as well as in numerous other cultures for thousands of years, and long predate the more recent development of pharmaceuticals over the past decades for the treatment of illness and disease. In a previous report, both TCM and a mango-leaf preparation were found to be effective in treating mild to moderate HTN.<sup>4</sup> Thus, the purpose of the present paper is to review the effectiveness of an herbal remedy consisting of mango flesh plus a mango leaf-ginger combination as a tea when added to a traditional multidrug therapeutic regimen for the management of hypertension in an adult male with well-controlled NIDDM but no other significant illnesses.

## **Overview of complimentary mechanisms of action of antihypertension pharmaceuticals and nutraceutical agents.**

### **Metoprolol Succinate**

Metoprolol is a beta-adrenergic receptor blocker agent, which impinges in vascular  $\beta_1$  and  $\beta_2$  adrenoreceptors to block the adrenergic effects of catecholamines, resulting in relaxation of vascular smooth muscle, thereby decreasing vascular resistance, and lowering of systolic and diastolic blood pressure. Metoprolol can be prescribed as monotherapy or in combination with other antihypertensive agents. Metoprolol is usually taken in the morning along with other medications.<sup>5</sup>

### **Losartan Potassium salt**

Losartan potassium is an antihypertensive agent that belongs to a class of drugs called angiotensin receptor blockers (ARBs). The ARBs bring about reductions in both systolic and diastolic blood pressure via inhibiting the hemodynamic effects of angiotensin, resulting in a relaxation of vascular smooth muscle and vasodilation, and lowering of vascular resistance such that peripheral blood flow may occur more easily. Because of the potassium content of losartan, plasma potassium concentrations

should be monitored periodically.<sup>5</sup>

### **Amlodipine**

Amlodipine belongs to a class of antihypertension agents called calcium channel blockers, which facilitates a relaxation of peripheral smooth muscle fibers, and decreasing the magnitude of cardiac work as a result of the peripheral vascular relaxation. Amlodipine may be used alone as monotherapy or in combination with other medications to hypertension in adults and youth over the age of 6 years. This agent can also be used to treat certain types of angina and coronary artery disease caused by narrowing of the coronary blood vessels. Accordingly, it can help to control symptoms of anginal chest pain by increasing the supply of blood to the heart. If taken regularly, amlodipine can control most anginal pain and discomfort, but it is effective only before as a preventive agent, but not after the anginal pain has occurred as caused by the coronary artery constriction and an impairment of coronary blood flow has commenced.<sup>5</sup>

### **Mango-ginger tea**

The blood pressure lowering effects of mango-ginger tea or mango flesh consumption on blood pressure are unclear but are presumed to be related at least in part to the micronutrient and antioxidant content of the mango leaves, which contain magniferin, a mineral and antioxidant rich constituent.<sup>6</sup> Mango leaves are routinely harvested from the common evergreen mango tree (*Mangifera indica* L), a member of the Anacardiaceae family. Mangos form part of an important tropical fruit crop from the Caribbean, and tropical regions of South and Southeast Asia, where they grow in abundance in part due to the mineral and nutrient rich soils found especially in volcanic soils common to the Caribbean and other tropical regions. In addition to harvesting and distribution of the Mango fruit, the leaves and decidua of the trees have been harvested for their naturally occurring phytotherapeutic potential. Mango leaves are the potential source of numerous minerals, including nitrogen, potassium, phosphorus, iron, sodium, calcium, magnesium, and vitamins A, B, E, and C. In addition, a major bio-macromolecule protein is also found in mango leaves, thereby adding to the nitrogenous nutrient content of the extracts and decoctions. Mango leaves and mango tree residuals resulting from tree husbandry activities are nontoxic and can be safely utilized as an alternative source of livestock feeding in developing countries for alleviating potential food shortages for livestock. Extracts of the mango leaves have been utilized for traditional medicines to treat numerous human illnesses including hypertension, diabetes, bronchitis, diarrhea, asthma, kidney, scabies, respiratory problems, syphilis, and urinary disorders.<sup>6</sup> Because the minerals occur in association with multiple organic residues, their luminal absorption is greatly improved when compared to non-organic mineral sources.<sup>7</sup> Magnesium

is a useful therapeutic agent to bring about muscle relaxation for both vascular and uterine smooth muscle, while also being a critical mineral for ATP regeneration and actions, where it has found several clinical uses in exercise physiology and other clinical applications.<sup>5,7</sup>

Ginger (from *Zingiber officinale* Roscoe) is the second major component of the mango-ginger tea and is a common and widely used spice that has abundant quantities of numerous bioactive and antioxidant compounds.<sup>8</sup> The bioactive compounds include polyphenols, terpenes, gingerols and shogaols, which are attributed to provide the major health-related benefits attributed to the spice. In addition to gingerols and shogaols, lesser concentrations of metabolically useful polysaccharides, lipids, organic acids, and raw fibers have also been found to occur in ginger. The bioactive antioxidant constituents of ginger are purported to function collectively to improve the cellular GSH/GSSG ratio, thereby enabling the antioxidant constituent to be able to quench excess inflammatory reactive oxygen species (ROS) activity, and which inflammatory actions may damage lipid membranes and other cellular constituents when left unquenched. Several investigations have demonstrated that ginger possesses multiple biological activities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, neuroprotective, cardiovascular protective, respiratory protective, antiobesity, antidiabetic, antinausea, and antiemetic activities that can contribute to metabolic processes and that may play important roles in maintaining human health.<sup>8</sup>

Thus, the combined impact of the above drug-nutraceutical combination is likely to enable vascular smooth muscle relaxation via a combination of adrenergic inhibition, angiotensin receptor blockade, magnesium, and calcium channel-mediated smooth muscle relaxation in addition to broad spectrum antioxidant and angiogenic activity when taken together. While each pharmaceutical agent individually can normally bring about limited vasodilatation and a reduction vascular resistance when taken as prescribed, usually in a once-a-day schedule, the combined impact of the multidrug plus nutraceutical regimen would be predicted to respond in an additive manner and extend the typical pharmacologic effects of the multidrug regimen when taken as monotherapy only.

## Methods

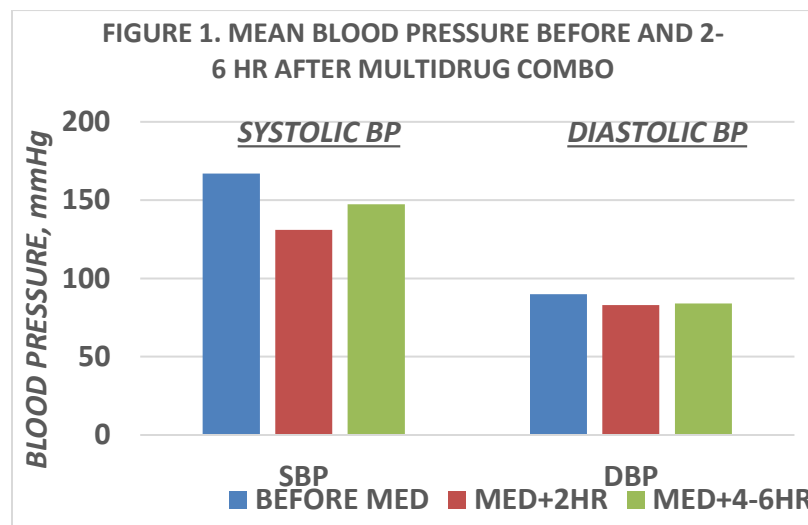
The patient was a middle-aged Caucasian male, age 65 yr. with well controlled Type II diabetes (HbA1c < 6.8), a BMI of 25, and mild to moderate hypertension and no other medically significant disorders. The combination multidrug treatment for hypertension consisted of

therapeutic dosages of 200 mg of metoprolol succinate (Extended-Release form), 50 mg of losartan potassium twice daily, and 5 mg of amlodipine was taken at 8AM (or 8 AM plus 8 PM daily where twice daily administration was prescribed), and the mango leaf-ginger tea (one serving) plus 6 slices (½ of a medium size fresh mango) were taken daily approximately 12 hours later, one hour prior to bedtime. All medications and nutraceutical agents were taken diligently and exactly as prescribed or recommended without exception. Treatment for NIDDM consisted of dietary control, in addition to metformin (1,000 mg daily) and glipizide (2.5 mg twice daily). Blood pressure monitoring was determined while sitting in a quietly resting state as outlined by Njoloma et al. (ref). All measures of SBP and DBP were taken by AAS with an electronic cuff (Health point USA, Blue Ocean Ecom Limited, Hillfoot, Formby Lane, Ormskirk, L39 7HG.) 2 to 3 times daily and recorded as mm of Hg. Data were plotted as the mean ±1 SEM were indicated and represent 4-6 repeated measurements during each week of the study with the Prism graphics program.<sup>8</sup> No adverse effects to the multidrug combination or to the mango leaf+ginger tea preparation were reported while conducting this case study.

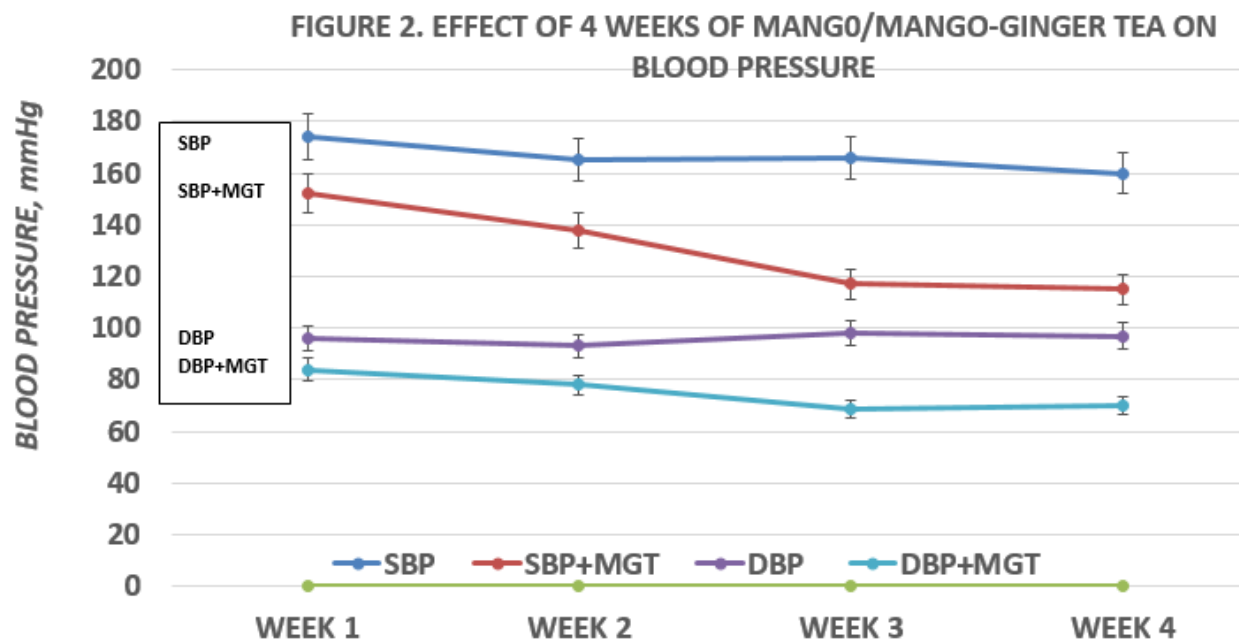
## Results

The results of the SBP and DBP measures before and after the multidrug administration are depicted in Figure 1 and indicate that both Systolic and Diastolic blood pressures reflected moderate hypertension, with consistent readings of greater than 140/80 mm Hg. In addition, values obtained after 2 and again after 4 to 6 hours post drug administration indicate that systolic pressures were decreased by an average of 22% after 2 hours, but the decrease was short-lived, as SBP measures were only reduced by 12% 4 to 6 hours after treatment and reverted back to fall within the hypertensive criterion for systolic pressures. The decreases on Diastolic BP were less significant following the multidrug treatment, having dropped modestly by only 7.8% after 2 hours and 6.7% after 4 to 6 hours post treatment, and thus were not of sufficient magnitude to fully normalize diastolic blood pressures based on medically acceptable criterion. The blood pressures obtained over the 4 weeks of drug treatment alone and the following four weeks of multidrug+mango leaf-ginger tea is depicted in Figure 2 below and indicate that both systolic and diastolic BPs remained stable averaging 165/96 over the four weeks of multidrug only observation when measures were obtained 6-12 hours post treatment.

Not shown in figure 2, the measures of SBP and DBP



**Figure 1.** Mean BP before and 2 hours and 4-6 hours after antihypertensive multidrug administration. Data are average of replicate determinations. SBP= systolic BP; DBP = diastolic BP; all BP measures are expressed in mmHg.



**Figure 2.** Data are mean of 3 to 6 replicate measure each week taken 6 to 12 hours after the pharmacologic regimen. The upper two lines represent the SBP (upper dark blue line) and SBP+MGT (red line) respectively and the lower two lines represent the DBP (Orange line) and DBP+MGT (lowest, lighter blue line) respectively. The average morning BP prior to administration of the multidrug treatment was 167/90 (n= 2 readings).

averaged 131/83 after 2 hours following the morning multidrug only administration, and only averaged a 12% decrease 4 to 6 hours following the multidrug administration. Following the introduction of the evening Mango snack plus the MGT beverage, however, the morning blood pressures of both SBP and DBP were reduced by 13% at week one, 17% at week two and averaged 30% reduction in both SBP and DBP measures in weeks three and four, thereby achieving their intended goal and reflecting a return to an essentially medically induced normotensive state by the end of the third- and fourth-week periods of observation.

## Discussion

Hypertension is a common condition and when left untreated, can serious and often life-threatening injury to the brain, heart, blood vessels, kidneys and other organs and tissues.<sup>1,9</sup> Hypertension is often referred to as a 'silent killer' as during the early stages of disease progression the individual may remain asymptomatic and may not recognize the subtle nature of early symptoms of an impending hypertensive or cardiovascular disorder. Numerous factors can contribute to the gradual progression of hypertension, including diet, exercise, excess weight gain, lifestyle practices, smoking, excessive alcohol consumption, comorbidities, and likely genetic predisposition. Monitoring the above factors within moderation alone can be partially if not wholly preventive in most individuals, and the strategic incorporation of a medication and therapeutic regimen tailored to the individual may slow or prevent the majority of further progression of hypertensive related disorders. For reasons that often remain unclear, medications as monotherapy or combination therapy of available treatment agents may not always bring about the desired return toward a normotensive state, thereby requiring the incorporation of adjustments in diet and lifestyle activities, to include consuming a diet that is low in fat, salt, and caloric content, developing a healthy weight, especially the lowering of visceral adipose tissue, exercising at least 30 minutes most days, not smoking, and using alcoholic beverages in moderation in addition to careful monitoring of the progression of comorbidities when present.<sup>9-12</sup>

The consumption of mango leaf tea is a common practice in certain parts of the world, including the Caribbean where nutrient rich volcanic soils are common and the presence of fruiting mango trees are often abundant.<sup>4,6,13</sup> The tea is prepared fresh by crushing a few fresh or dried mango leaves in a liter or so of water, steeping for about 15 minutes or just left overnight in room temperature water in order to extract the water soluble elements and is deemed sufficient to extract the essential principles from

the leaves. The tea may be consumed as soon after preparation as is desired and is usually consumed while freshly prepared and still warm and pleasant to the taste.<sup>4,13</sup> While natural or artificial sweeteners such as natural honey may be added to taste, they usually are not required. The mango-ginger tea used in the present case study is a useful modification of the traditional Caribbean mango leaf tea in that the Ginger provides additional antioxidant properties that can address potentially malevolent issues of inflammation in peripheral tissues, especially when inflammation-prone visceral fat stores are increased, and thus complement the nutraceutical impact of the mango leaf extract provided by the addition of ginger to the tea. By incorporating the tea into an allopathic pharmaceutical multidrug regimen, the tea can add effectively additional vital phytochemically-mediated elements to the overall mechanisms of action that the base regimen may not have incorporated or recognized.

In studies of the efficacy of natural products and losartan, Lai et al<sup>12</sup> evaluated a traditional Chinese natural product remedy in a large cohort of patients (over 1000 patients in all) with mild to moderate hypertension, who were taking either the TCM or the losartan regimen and found the outcomes to be equivalent to those of a daily 50 mg dosage of losartan in controlling both systolic and diastolic pressure.<sup>12</sup> In another study by conducted by Chow et al<sup>13</sup> the authors also reported a similar outcome success when comparing a traditional ancient TCM regimen (THSWT or SWT) to allopathic medications in patients with mild to moderate hypertension, and Tulp et al reported a case study that demonstrated the efficacy of mango leaf tea as monotherapy in controlling markers of mild to moderate hypertension in Montserrat in the absence of availability allopathic medications, and where the consumption of locally-prepared mango leaf tea is common.<sup>13</sup>

In the present case study reviewed above, it became apparent that the single daily dosage of the allopathic medication combination was inadequate to provide effective 24-hr control of blood pressure measurements, with the effectiveness of the regimen beginning to wane within 4 to 6 hours after morning drug administration, suggestive of early drug clearance, multidrug resistance or some combination of the two factors. While the multidrug regimen provided effective systolic blood pressure control in the early hours following administration, diastolic blood pressures reflective of peripheral vascular resistance, were only partially normalized during the first 2 hours, but also returned to pretreatment levels later in the day. Thus, the multidrug regimen when taken alone as typically prescribed was not completely successful in effective clinical management of hypertension throughout the day and evening as the therapeutic half-life of the dosages



administered appeared to have been inadequate for an optimal outcome to have occurred. Were the dosages adjusted to higher levels or if additional antihypertensive agents or repeat dosages were to be added to the regimen, the potential for adverse side effects of the multidrug combination would also likely have necessarily increased. Thus, the decision to incorporate modest quantities of a naturally occurring nutraceutical agent with no known side effects when consumed as directed to the partially effective multidrug regimen was deemed a reasonable clinical course of action in an attempt to improve hypertensive parameters over a longer duration. The mango leaf-ginger combination was selected due to the antioxidant and micronutrient properties of the tea, which would then incorporate yet an additional mechanism of action to the multidrug combination therapy in addition to the reported efficacy of the tea as a monotherapy in managing hypertension of mild to moderate severity. While the pharmacologic agents each typically report a single mechanism of action, the mango leaf+ginger tea contains a plethora of antioxidant and micronutrient constituents which when combined with the allopathic agents, was observed to extend the mechanism and effective duration of action in such manner that vascular elasticity and peripheral resistance appears to have become improved, thereby enhancing the effectiveness of the allopathic agents. The ginger component in combination with the micronutrients has also been reported to increase the process of angiogenesis, thereby further enhancing the clinical effectiveness of the nutraceutical addition to the antihypertension regimen and suggest that additional trials of a longer duration may be helpful and perhaps may help lead to a further explanation of the complex mechanisms of action implicated in the vascular responses and in the pathophysiologic contributors to hypertension.

## Conclusion

The results of this clinical case study indicate that the addition of a commonly available Mango Leaf+ Ginger tea plus mango fruit flesh to a multiagent allopathic regimen for the management of moderate hypertension was effective in improving the clinical outcome of the hypertension parameters after a loading time duration of 2 to weeks of observation. The blood parameters demonstrated moderate improvement beginning within one week of observation, additional improvement at the 2-week marker, and which resulted in sustained normalization of both systolic and diastolic blood pressures after 3 and 4 weeks of observation. Although the parameters of NIDDM were not specifically included in the study they remained in adequate control throughout the study. The physiologic basis for the nutraceutical-mediated improvements is unclear and could not be determined from the study but are presumed to be due at least in part to the broad phytochemical content of the

mango leaf and ginger components, which are well established to reduce excess ROS activity and to augment antioxidant reducing activity in peripheral tissues while enabling improvements in physiologic parameters over time. The basis for the incomplete clinical management of hypertension with the aggressive multidrug regimen undertaken remain unclear but may be linked at least in part to prior vascular pathophysiologic processes which may have occurred secondary to the longstanding NIDDM which was also present. Because NIDDM is an established risk factor for hypertension, even when adequate plasma glucose control measures have been incorporated into a patient's treatment plan, the NIDDM likely contributed at least in part to the clinical outcome in this individual.<sup>2</sup> Like hypertension, symptoms of NIDDM contribute to peripheral vascular injury and also may be unrecognized during the early stages of development of the disorder and thus may result in additional complications in later attempts for clinical management of pathophysiologic NIDDM sequela. The Mango leaf – ginger tea provided magniferin, antioxidants, and numerous micronutrients and phytochemicals that are conducive to improving parameters human health.

## Acknowledgement

The authors thank the University of Science Arts and Technology, Montserrat for the generous donation of fresh mango leaves and Institutional Resources to support this study.

## Conflict of Interest

We have no conflict of interests to disclose and the manuscript has been read and approved by all named authors.

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