Archives of Nephrology

ISSN: 2639-3573

Volume 3, Issue 2, 2020, PP: 38-48

Kidney Injury, Polyherbal Therapy and "Triple Whammy": Trends in Covid-19 Pandemic

Christopher E. Ekpenyong[1]*, Ernest E. Akpan[1]

[1]Department of Physiology (Cardio-Renal Unit), Faculty of Basic Medical Sciences, University of Uyo, Uyo, Nigeria.

***Corresponding Author:** Christopher Edet Ekpenyong, Department of Physiology, Faculty of Basic Medical Sciences, University of Uyo, Uyo, Nigeria.*

Abstract

***Introduction:** During the recent global outbreak of the COVID-19 pandemic, an interesting trend was observed: the combination of various herbs in the bid to prevent or even ameliorate the symptoms associated with COVID-19. Herb-drug/herb-herb interaction has been a key culprit in the etiology of progressive kidney injury. With the mounting interest in combination or polyherbal therapy to achieve therapeutic benefits for several diseases, there is a need to explore more on herb-herb and herb-drug interaction on different body systems.*

This review article focused on medicinal herbs with diuretics, anti-inflammatory/analgesic, and angiotensin-converting enzyme inhibitory (ACEI)) activities that could be associated with the etiology of the Triple Whammy Phenomenon.

***Methods:** Our search utilized the PUBMED and Science Direct databases and the inclusion criteria were based on the following keywords and phrases: triple whammy, herbal medicine, medicinal herbs with a diuretic, anti-inflammatory/analgesic, and angiotensin-converting enzyme inhibitory (ACEI)) activities.*

***Results:** Some commonly used medicinal herbs have been shown from in vivo or in vitro studies to possess diuretic, angiotensin-converting enzyme inhibitory, and anti-inflammatory prowess.*

***Conclusion:** Patients who unknowingly take large quantities of these herbs and for a long duration might experience changes in intra-renal autoregulatory hemodynamics with a resultant renal dysfunction.*

Keywords: *Herbal medicine, acute renal dysfunction, polyherbal combinations*

Introduction

Over the last decades, the use of herbal-based therapy, and in particular poly-herbal mixture as a therapeutic modality has significantly increased and is becoming widely accepted. [1] A greater percentage of the population in developed and developing nations have resorted to Complementary and Alternative Medicine (CAM) for treatment purposes, and herbal medicine forms a chunk of its application. [2]

Current data indicate that >200,000 natural products of plant origin are known and are used either as a mono-herbal or poly-herbal mixture, and many more are being identified from higher plants. [3, 4, 5]

The wide acceptance of herbal-based therapy would not be far from the fact that herbal medicine is a cheaper alternative with perceiving fewer undesired side effects. [1, 6, 7, 8] The rationale for the use of herbal remedies is not surprising, because they contain thousands of bioactive components that have known therapeutic applications. [9] Indeed, herbs have provided a starting point for the synthesis of over 50% of currently used pharmaceutical drugs. [9, 8]

With the increasing acceptance of herbal remedy, several hundreds of plants which initially were considered to be safe and therefore extensively consumed are now showing some toxic manifestation in some vital organs such as kidneys, skin, brain, heart, and liver especially on prolong ingestion, raw usage and or repeated exposure. [10] Some of these

natural products either as mono-herbal or poly-herbal mixtures contain active compounds with a diuretic, anti-inflammatory/analgesic, and angiotensin-converting enzyme inhibitor (ACEI) / or angiotensin II receptor blocker's (ARB) activities which can cause changes in intra-renal autoregulatory hemodynamics with a resultant renal dysfunction similar to the effects of synthetic diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), ACEI/or ARBs and patients who unknowingly take large quantities or prolonged use of herbs with these properties might develop renal dysfunction. The nephrotoxicity is worsened if a mixture of herbs with these properties is consumed due to the "Triple Whammy phenomenon".

Factors such as age (>60yrs), pre-existing dehydration, gender, co-existing disease condition e.g., congestive cardiac failure (CCF), increase blood pressure, nephrotic syndrome (NS), variability in active/toxic ingredients, overdose, prolonged use/abuse, drug-herb interaction, an idiosyncratic reaction could account for the different systemic untoward effects associated with herbal therapy [10]. Diverse empirical data shows that the use of herbal medicinal products by patients especially older ones is on the rise and that typically a combination of different herbal products is used at a time, often concomitantly with prescription medicines. Older patients are reluctant to tell their physicians that they are taking herbal products and so are at risk of potential drug-herb interactions. [11,12, 13]

Whilst the complementary treatments may offer considerable benefits for a spectrum of conditions, caution is needed, particularly concerning potential drug-herb interactions and possible adverse effects, when herbal medicinal products are used by older patients and individuals with compromised renal status.

This review article focuses on medicinal herbs or poly-herbal mixture with diuretics, anti-inflammatory/ analgesic, ACEI and ARB activities which are associated with adverse renal endpoints ("*Triple Whammy Phenomenon").*

The Triple Whammy Phenomenon

The Triple Whammy phenomenon describes a triple-drug combination-induced renal failure due to a simultaneous three-fold adverse effect on renal endpoints [14]. It results from the combination of ACEI or ARB, diuretic, and NSAIDs or COX-2 inhibitor particularly in the elderly. [14, 15]

When used individually or in combination, this trio has been implicated in more than half of the reported iatrogenic acute renal failure occurrences. As a matter of caution, it is advised that this trio of medications should be avoided particularly among high-risk persons for renal disease such as those with severe dehydration, diabetes mellitus, high protein diet, renal compromised state, and during vulnerable periods such as during renal dialysis, renal transplant, and those on prescription medications known to harm the kidney such as aminoglycoside antibiotics, and anti-retroviral drugs. As a rule of thumb, to prevent the triple whammy phenomenon is by avoiding NSAIDs. When an ACEI /ARB with a diuretic is prescribed, patients were advised to avoid NSAIDs. [15, 14]

The elderly and people with co-morbidities such as heart failure or severe liver disease or dehydration from acute illness have an increased risk of acute kidney injury (AKI). [16, 17] Empirically, ACEI, and NSAIDs have been reported to adversely affect renal blood flow while diuretics have the potential to cause dehydration. Individually, these medicines affect renal function, either directly or indirectly; a 'double whammy' or a 'triple whammy' can be harmful if individuals have predisposed underlying risk factors for acute kidney injury (AKI).

Further, NSAIDs antagonize beneficial antihypertensive effects of ACEI and diuretics in people with heart failure. [14, 17] Older adults are especially vulnerable to the *Triple Whammy* because they often have a degree of pre-existing renal impairment. [18] Other reasons may include sensitivity to the renal effects of NSAIDs, inadequate fluid intake, and being prone to diuretic-induced dehydration and hypotension. [18] Several different mechanisms have been implicated in the pathogenesis of the *Triple Whammy* phenomenon. They include inhibition of both prostaglandin-mediated control of glomerular afferent arteriolar tone and angiotensin control of efferent arteriolar tone. Additionally, diuretics decrease the plasma volume, thus reducing renal plasma flow (Figure 1). [19]

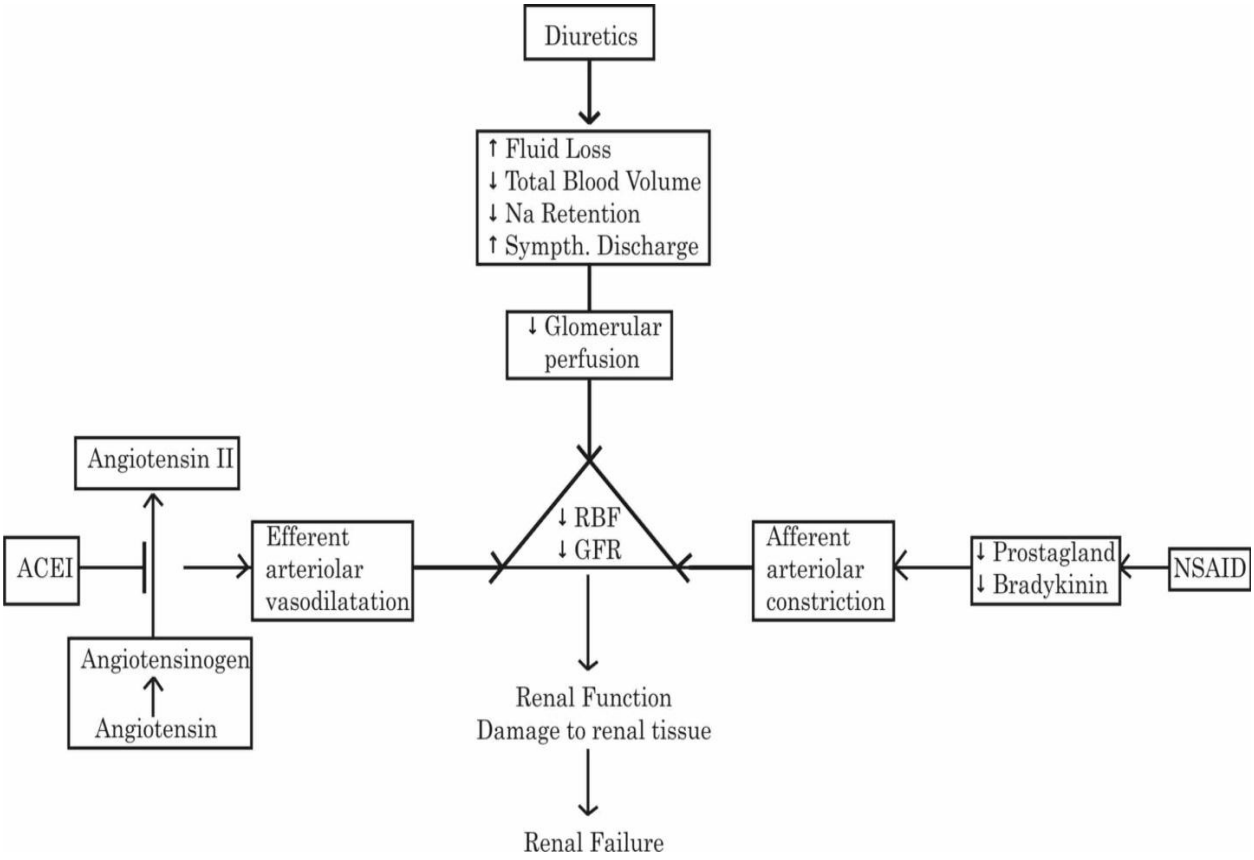

Figure1. *Schematic representation of the pharmacodynamic synergism of diuretic, anti-inflammatory, and angiotensin-converting enzyme inhibitory effects ("Triple Whammy") leading to acute kidney injury. (NSAID=Nonsteroidal Anti-inflammatory Drugs, RBF= Renal Blood Flow, GFR= Glomerular Filtration Rate, Na= Sodium).*

Herbs with Anti-Inflammatory/Analgesic Properties

Phytochemicals such as flavonoids (flavanols {eg., kaempferol, quercetin, myricetin}; flavones {eg., apigenin, luteolin}; flavanones {eg., hesperetin}; flavanols {eg., catechin}; anthocyanidins {eg., pelargonidin, cyanidin}; and isoflavones {eg., daidzein, genisten}) xanthones, saponins, alkaloids, coumarin, tannins, withaferin-A, andrographolide, and sterols, found in fruits, seeds, leaves, roots and barks of herbs have proved to exert potent anti-inflammatory activities. [20, 21, 22]

For example, flavonoids have been shown to exert anti-inflammatory activities by inhibiting the production of inflammatory mediators by modulating the arachidonic acid pathway, inhibiting several enzymes such as adenosine triphosphatase, prostaglandin, cyclooxygenase, lipoxygenase, nicotinamide adenine dinucleotide-hydrogen, oxidase, protein kinase, hydrolases, peroxidases, metallopeptidases, tyrosinases, and phospholipases. [23, 24] Additionally, flavonoids act by modulating the induced nitric oxide synthase enzyme and the cells involved with inflammation, inhibiting the production of proinflammatory cytokines and modulating the activity of arachidonic acid pathways, such as lipoxygenases (LOX), cyclooxygenase (COX), and phospholipase A2. [25]

Table 1 shows some common plants with anti-inflammatory activities used traditionally and reported in the literature.

Herbs with Diuretics Properties

In folklore, medicinal herbs are a significant source of natural diuretics. Diuretics are used in the treatment of cardiovascular and renal diseases including hypertension, congestive cardiac failure, some renal diseases associated with abnormal accumulation of fluid (Oedema) e.g., nephrotic syndrome.

Naturally occurring phytochemicals with diuretic properties such as saponins, tannins, flavonoids, and caffeine are found in herbs. They work within the kidney to promote the excretion of urine and sodium from the body through various mechanisms, and these results in the reduction of the circulating blood volume. Diuretics work by interfering with the re-absorption of ions (Na+, K+, Ca2+, and Cl-), and water through the walls of the kidney tubules. [26] For instance, in studies by Pantoja *et al.,* [27] and Dearing *et al.,* [28] saponins, tannins, and flavonoids induced diuresis and natriuresis through the inhibition of Na^+, and Na^+, K^+, ATPase activities at the Na^+ re-absorption level of the kidney similar to other standard loop diuretics.

In a similar study, deSouza *et al.,* [29], compared the diuretic effect of saponins with that of furosemide and found that the diuretic efficacy of saponins was comparably higher than that of furosemide, a standard diuretic which also acted by inhibiting the 3-ion co-transporter system (Na+/K+ 2Cl-). [30] Jouad *et al.,* [31] in a study to compare the effect of flavonoids and furosemide on blood pressure found that flavonoids exerted a significant diuretic action similar to furosemide and double the effect of placebo.

Physiological mechanisms indicate that prolonged diuresis could induce excessive Na+ loss and a marked reduction in plasma and extracellular fluid (ECF) volume with a resultant cascade of biochemical and physiological changes; including activation of neural, hormonal, and local mechanisms leading to enhance baroreceptors activity and renal sympathetic tone, increase catecholamine levels and increase the activity of the rennin-angiotensin system and other vasoconstrictor systems. [32] These could result in the reduction of glomerular filtration rate (GFR) and by extension other renal function indices. Table 1 shows some common plants with diuretic properties used traditionally and reported in the literature.

Herbs with Angiotensin-Converting Enzyme Inhibitory (Acie) Effects

The therapeutic maneuver in the activities of renin, ACEI, and/or ARB is cardinal to the management of high blood pressure, congestive heart failure, and diabetic nephropathy. Many available herbs have shown potent ACE inhibitory potency and have been in use in the management of cardiovascular disorders such as hypertension. They are favorably used due to both their antioxidant and ACE inhibitory prowess. Food plants such as garlic, cinnamon, grapefruits, berries, jasmine, etc. have been shown to possess blood pressure-lowering prowess via different mechanisms including ACEI. [33]

Epidemiological studies have drawn trend lines linking the correlation between garlic consumption and reduction of systolic and diastolic blood pressure [34, 35] and ACEI prowess due to its allicin contents. [36, 37] Other secondary bioactive constituents synthesized in plants such as flavonoids, xanthones, procyanidin, hydrolyzable tannins, caffeoylquinic acid derivatives have been reported to be effective ACEIs. [38, 39]

Table 1 shows some other common plants with ACE inhibitory prowess used traditionally and reported in the literature.

Table1. *Comparison of Herbs with Two or Three of the Indicators for Triple Whammy*

S/N	Botanical name	Common name	ACE Inhibitory Action	Anti-inflammatory action	Diuretic action	References
1	*Allium cepa*	Onions	✔	✔	✔	[40]
2	*Allium sativum*	Garlic	✔	✔	✔	[27, 41, 33, 42]
3	*Aloe vera*	Aloe vera	✔	✔	✔	[42]
4	*Ananas comusus*	Pineapple	✔	✔	✔	[16]
5	*Carica Papaya*	Pawpaw	✔	✔	✔	[43]
6	*Citrus aurantiifolia*	Lime	✔	✔	x	[37]
7	*Citrus lemon*	Lemon	✔	✔	✔	[44]

8	*Coffae Arabica L*	Coffee	✔	✔	✔	[45, 46, 47, 48]
9	Crataegus microphylla C. Kosh	An Hawthorn species	✔	**x**	✔	[49]
10	*Cymbopogon Citratus*	Lemon grass	✔	✔	✔	[50, 51, 52]
11	*Cynodon dactylon(l)*	Scotch grass/ Bermuda grass	✔	**x**	✔	[49]
12	*Echinacea purpora(l) moench*	Purple cone flower	✔	✔	**x**	[49]
13	*Foeniculum Vulgare*	Fennel	✔	✔	✔	[49]
14	*Gingko biloba*	Gingko	✔	✔	**x**	[42]
15	*Hibiscus sabdariffa*	Roselle	✔	✔	✔	[53, 54, 55, 56, 57, 22]
16	*Hypericum perforatum*	St. John Wort	✔	✔	✔	[58]
17	*Lactuca Scariola*	Prickly lettuce	✔	✔	✔	[49]
18	*Moringa oleifera Lam*	Moringa	✔	✔	✔	[59]
19	*Morinda citrifolia*	Noni fruit	✔	✔	✔	[60]
20	*Nigella sativa*	Black Cumin	✔	✔	✔	[61, 62, 24]
21	*Nymphaea alba L*	White water lily	✔	✔	✔	[49]
22	*Occimum Basilicum*	Basil	✔	✔	✔	[40]
23	*Onopordum Acanthium*	Cotton thistle	✔	✔	✔	[49]
24	*Panax ginseng*	Ginseng	✔	✔	**x**	[63, 64]
25	*Zea Mays L*	Maize	✔	✔	✔	[49]
26	*Zingiber Officinalis*	Ginger	✔	✔	✔	[49]

x = Insufficient report in literature
✔= Reported in Literature

Principles/Rationale for Polyherbal Combination

Herbal medicine has been an integral component of medicine whose origin dates back to over 2000 years behind us. Phyto-medicine has its roots intertwined in diverse cultures such as China, South East Asia, and Africa. The herbal formulation that contains two or more combinations is known as Polyherbal formulation. More specifically, the herbal formulation is based on two cardinal principles: the use of a single herb and the use of two or more herbs. [65]

Historically, Ayurveda spotlighted the entire concept of synergism in the use of polyherbal formulation. Even though single or monoherbal formulation has shown potency due to its active phytoconstituents, they are insufficient to achieve the desired therapeutic effects. Scientific studies have revealed that plants of diverse potency when combined may in principle produce a greater result as compared to individual use of the plant, and also the sum of their individual effects, this positive herb-herb interaction produce synergism and pharmacodynamic synergism. [66, 65]

With the mounting interest in shifting from one drug or to one target paradigm to a combination or polyherbal therapy to achieve therapeutic benefits for several diseases, there is a need to explore more on herb-herb and herb-drug interaction. For example, in Chinese medicine, the practice of poly-herbalism is based on the principles of reinforcement, potentiation, counteraction (or antagonistic interaction), restraint & detoxification, and incompatibility. Interestingly, they are further functionally classified as "*emperor*", "*minister*", "*assistant*" and "*servant*" herbs [67]. It is opined that the toxicity of plant extract is reduced when whole herb parts are used instead of isolated active phytoconstituents buffering thereby enhancing efficacy and reducing adverse effects. [68]

Herb-Drug Combination and "Triple Whammy": Current Trend

Increased use of herbal medicine by patients alongside their prescription drugs irrespective of the underlying disease conditions continues to raise concerns of noncompliance in medical practice. [69] It is not surprising that despite a repeated admonition from physicians, patients still combine orthodox drugs with herbs thereby ignorantly incurring the 'wrath of progressive renal impairment'. This herb-drug interaction has been a key culprit in the etiology of progressive kidney injury.

Although the practice of polyherbal combination is seen to be innocuous by a few adherents of phytomedicine, what if these combinations exert beneficial succor to one system and exert a negative impact on another, acting like the *paradoxical poisonous panacea*. There are reports of nephrotoxicity associated with some herbal medications due to factors not limited to: contamination by heavy metals, intrinsic toxicity of herbs, and addition of toxins, incorrect identification, processing, and storage. Other factors such as over-dosage, herb-drug interaction, and patient-related factors (such as gender, age, allergy, and underlying risk factors for kidney diseases) [70] have been associated with the etiology of kidney impairment. Based on age and gender, it is observed that the use of herbs is common among the elderly (aged 65 and above) and women in the adult population than men. [71]

Poly-Herbal Therapy and "Triple Whammy": Trends in Covid-19 Pandemic

During the recent global outbreak of the COVID-19 pandemic, an interesting trend was observed: the dread of SARS-CoV-2 stirred so much research and counter investigations in a bid to stem the tide of COVID-19. [70] From that instance, an unrelenting search for a panacea went into motion.

Also, the consumption of poly-herbal mixture increased, especially those known to possess anti-inflammatory/analgesic, immune-modulating, ACEI/ ARA effects, which may also have a diuretic effect, in the bid to prevent or even ameliorate the symptoms associated with COVID-19 by boosting one's immunity, provide anti-inflammatory and analgesic effects or on other the hand cure the corona virus. Literature evidence indicates that herbs such as Curcuma Xanthorrhiza, Echinacea purpurea, Cinchona species [72] were consumed for the prevention of the effect coronavirus infection. Some of these herbs are known to have a "Triple Whammy" effect, and either alone or in combination can alter the renal auto-regulatory hemodynamics and hence, exert negative effects on renal endpoints.

Also, many foods and herbs have been shown to possess antiviral, anti-influenza, immunomodulating prowess, and have activities against severe acute respiratory syndrome coronavirus such as Glycyrrhiza radii, Lycoris, extracts of Scythian Lamb rhizome, Lianhuaqingwen, [73] aloe vera, ginseng, garlic, cinnamon, bergamot, and lemongrass among the few were subjected to a clinical trial. [74] It is the wish of the research community that a sustainable panacea to the pandemic is found which could be natural based and without other systemic untoward effects.

Poly-Herbal Therapy and "Triple Whammy" Trends in Non-Communicable Disease

The web of non-communicable disorders such as hypertension, diabetes mellitus and other metabolic disorders and associated renal disorder is on the rise globally. The classes of herbs/ drugs commonly used in the treatment of hypertension and heart failure, and often in combination are diuretics, ACEIs /or ARBs, anti-inflammatory drugs (e.g., non-steroidal anti-inflammatory drugs (NSAIDs)). The

frequency, duration, and ease with which they are concurrently prescribed and used by these patients and the increasing burden of acute and chronic kidney diseases in all regions of the world and associated cardiovascular deaths create a significant public health concern.

As shown in table 1, some commonly used medicinal herbs have been shown from *in vivo* or *in vitro* studies to possess diuretic, ACEI, and anti-inflammatory prowess which in principle could cause changes in intra-renal auto-regulatory hemodynamics with a resultant renal dysfunction similar to the effects of synthetic diuretics, NSAIDS, ACEI/or ARBs and patients who unknowingly take large quantities or prolonged use of herbs with these properties might develop renal dysfunction. Some of the herbs highlighted in the table 1 possessed two out of the three while others had all three properties, a more reason why caution should be taken when combining these herbs.

When ACE inhibitors or ARB's drugs are administered alone, they generally preserve renal functions. However, they could decrease GFR by causing efferent arteriolar vasodilatation while diuretics can also contribute to acute kidney injury (AKI) by causing increase fluid loss, decrease total blood volume, decrease sodium retention, increase sympathetic discharge, hypovolemia, decrease glomerular perfusion, decrease renal blood flow, and ultimately decrease GFR and other renal endpoints. [75] The co-administration of NSAIDs aggravates the condition by the blockage of the COX-2 enzyme thus preventing prostaglandin synthesis which would result in afferent arteriolar vasoconstriction. [75] It is worth noting that the risk of AKI is higher in the first months of NSAIDs and results as a complication of hypovolemia and sepsis and should be suspected in all patients who for any reason combine the trio medications. [76]

Conclusion

Just as it is for the synthetic drugs, to avoid the possible complications associated with the triple whammy phenomenon, [77, 78] the following should be considered when combining herbs with ACEIs, diuretic, COX-2 inhibitory properties for any health condition including hypertension: any stage of chronic kidney disease, persons older than 65 years of years, persons experiencing volume depletion (due to vomiting, diarrhea, and sepsis), with heart failure, liver diseases or of certain ethnicity (Maori, Pacific, and Indo Asian.

In principle, whenever medicinal herbs are used for the management of any ailment, the change in body weight, blood pressure, serum creatinine, and electrolytes should be closely monitored. It is in the best interest to take baseline values of body weight (markers of dehydration), blood pressure, and especially serum creatinine levels before any polyherbal based administration. Additionally, thirst, lethargy, orthostatic hypotension, reduced urine output, dry mucous membrane, decreased skin turgor are said to be signs of AKI due to hypovolemia. As a point of preference, restoration of fluid balance and withdrawal from nephrotoxic herbs are immediate goals of care if patients develop triple whammy adverse effects.

References

[1] Frishman WH, Beravol P, and Carosella C. Alternative and complementary medicine for preventing and treating cardiovascular disease. Dis Mon 2009; 55: 121–192.

[2] WHO (2008).*Traditional Medicine.* Geneva: World Health Organization Fact SheetNo134.

[3] Ekpenyong CE. Transient Hyperbilirubinaemia and Sustained Elevation of Alkaline Phosphatase after the Ingestion of *Lemongrass tea.* Elixir Physiology and Anatomy 2016; 100: 43512-43516.

[4] Lee KH. Novel antitumor agents from higher plants. Med Res Rev 1999; 19: 569-596.

[5] Kinghorn AD, Pan L, Fletcher JN, Chai H. The relevance of higher plants in lead compound discovery programs. J Nat Peod 2011; 74: 1539-15555.

[6] Susalit E, Agus N, Effendi I, Tjandrawinata RR, Nofiarny D, Perrinjaquet MT, Verbruggen M. Olive (Oleaeuropaea) leaf extract effective in patients with stage-1 hypertension: comparison with Captopril. Phytomedicine 2011; 18: 251-258.

[7] Tabassum N and Ahmad F. Role of natural herbs in the treatment of hypertension. Pharmacogn Rev 2011; 5: 30–40.

[8] Al Disi SS, Anwar MA and Eid AH. Anti-

hypertensive Herbs and their Mechanisms of Action: Part I Front Pharmacol 2016; 6: 323.

[9] Pan SY, Zhou SF, Gao SH, Yu ZL, Zhang SF, Tang MK, Sung JN, Ma DL, Han YF, Fong WF, Ko KM. New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. Evidence-Based Complementary and Alternative Medicine 2013: 627375

[10] Ekpenyong CE, Akpan EE, Udoh NS. Phytochemistry and toxicity studies of *Telfairia occidentalis* aqueous leaves extract on liver biochemical indices in Wistar rats. American Journal of Medicine and Medical Sciences 2012; 2(5): 103-110

[11] Foster DF, Phillips RS, Hamel MB, Eisenberg DM. Alternative medicine use in older Americans. Journal of the American Geriatrics Society. 2000; 48: 1560–1565

[12] Canter PH, Ernst E. Herbal supplement use by persons aged over 50 years in Britain. Drugs Aging 2004; 21(9): 597–605.

[13] Raji MA, Kuo YF, Snih SA, Sharaf BM, Loera JA. Ethnic differences in herb and vitamin/mineral use in the elderly. Ann Pharmacother 2005; 39(6): 1019-23.

[14] Thomas MC. Diuretics, ACE inhibitors and NSAIDs- the triple whammy. Med J Aust 2000; 172: 184-5.

[15] Mathew T. Drug-induced renal disease. Med J Aust 1992; 156: 724–8.

[16] Adams RJ, Appleton SL, Gill TK, Taylor AW, Wilson DH, Hill CL. Cause for concern in the use of non-steroidal anti-inflammatory medications in the community-a population-based study. BMC Fam Pract 2011; 12: 70.

[17] Waitemata District Health Board. The Tripple Whammy - Safe Prescribing - A Dangerous trio. Accessed from www.saferz.co.nz/full/tripplewhammy.pdf on September 10, 2020.

[18] Savage R. CARM reports acute renal failure. Best Practice Journal 2007; 6: 26-7

[19] Greger R. Physiology of renal sodium transport. Am J Med Sci 2000; 319: 51–62.

[20] Rajkapoor B, Burkan ZE, Senthilkumar R. Oxidants and human diseases: Role of antioxidant medicinal plants - A review. Pharmacology Online 2010; 1: 1117–1131.

[21] Singh B, Sharma RA. Plant terpenes: Defense responses, phylogenetic analysis, regulation and clinical applications. Biotech 2014; 5: 129–151.

[22] Hussein ME, El Senousy AS, El-Askay HI, Moueir SM, and El-Fishawy AM. Immunomodulatory and anti-inflammatory activities of defatted alcoholic extract and mucilage of *Hibiscus sabdariffa* l leaves, and their chemical characterization. Journal of Pharmacognosy and Phytochemistry 2019; 8(4): 982-990.

[23] Rex JRS, Muthukumar NMSA, Selvakumar PM. Phytochemicals as a potential source for anti-microbial,anti-oxidant and wound healing—A review. MOJ Bioorg Org Chem 2018; 2: 1.

[24] Nunes C, Arantes M, Pereira S, da Cruz L, Passos M, de Moraes L, Vieira I&2, and de Oliveira D. Plants as Sources of Anti-Inflammatory Agents, Molecules 25; 3726

[25] Bassiouni W, Diabetes T, LouedecL NX, Senbel AM. Evaluation of some prostaglandins modulators on rat corpus cavernosum *in-vitro*: Is relaxation negatively affected by COX-inhibitors? Biomed Pharmacother 2019; 111, 1458–1466.

[26] Brater DC. Pharmacology of diuretics. American J Medical Sciences 2000; 319(1): 38-50.

[27] Pantoja C, VMartín NT, Norris BC, Contreras CMP. Urification and bioassays of a diuretic and natriuretic fraction from garlic (*Allium sativum*). Journal of Ethnopharmacology 2000; 70: 35-40.

[28] Dearing MD, Mangione AM, Karasov. Plant Secondary compounds as diuretics: overlooked consequences. American Zoology 2001; 41: 890-901.

[29] deSouza AM, Lara L, Previato JO, Lopes AG, Caruso NC, de Silva BP, Parente JP, 2004. Modulation of Sodium pumps by steroidal saponins. Zeitschrift for Naturforschung C 2001; 59: 432-436.

[30] Sadki C, Hachi B, Souliman A, Atmani F. Acute diuretic activity of aqueous Eric multiflora flower and Cynodn dactylon rhizomes extract in

rats. Journal of Ethno-pharmacology 2010; 128: 352-356.

[31] Jouad A, Lacille-Dubois MA, Eddouks M. Chronic diuretic effect of the water extract of Spergulaia purpurea in normal rats Ethnopharmacol 2001; 75: 219-223..

[32] Ekpenyong CE, Daniel NE, Antai AB. Effect of Lemongrass Tea Consumption on Estimated Glomerular Filtration Rate and Creatinine Clearance Rate. Journal of Renal Nutrition 2015; 25 (1): 57-66.

[33] Kamrani R, Jelvadi B, Hayes AW, Karim G. Potential angiotensin-converting enzyme (ACE) inhibition from traditional plants described in Avicenna Cannon of Medicine. Avicenna Journal of Phytomedicine 2019; 2(4): 291-309

[34] Ried K, Fakler P. Potential of garlic (Allium Sativum) in lowering high blood pressure: mechanisms of action and clinical relevance. Integrated Blood Pressure Control 2014; 7: 71-82.

[35] Xiong X, Wang P, Li S, Li X, Zhang Y, Wang J. Garlic for hypertension: a systematic review and meta-analysis of randomized controlled trials. Phytomedicine 2015; 22: 352-361.

[36] Shouk R, Abdou A, Shetty K, Shaker D, Eid AH. Mechanism underlying the antihypertensive effects of garlic bioactive. Nutr Res 2014; 34: 106-115.

[37] Oboh G, Akinyemi AJ, Ademiloyi AO. Inhibitory effects of phenolic extract from garlic on angiotensin-converting enzyme and cisplatin-induced lipid peroxidation. Int J Biomed 2013; 98-106

[38] Kang DG, Kim YC, Sohn EJ, Lee YM, Lee AS, Yi, MH, Lee HS. Hypotensive effect of buttein via inhibition of the angiotensin-converting enzyme. Biol Pharm bull 2003; 26(9): 1345-7

[39] Loizzo MR, Said A, Tundis R, Rasheed K, Statti GA, Hafner A, Menichi F. Inhibition of the angiotensin-converting enzyme (ACE) by flavonoid isolated from Ailanthus excels (Roxb). Phytotherapy Res 2007; 21: 32-6

[40] Perez M, Boffil MA, Moron FJ, Sueiro ML, Marrero E *et al*. Eir J Food Agric 2011; 23(3): 214-221.

[41] Dutta K, Chetia P, Lahkar S, Das S. Herbal Plants Used as Diuretics: A comprehensive review. Journal of Pharmaceutical, Chemical and Biological Sciences 2014; 2(1): 27-32

[42] Chaudhary, N, Sabikhia, L, Hussaina S, Sathish H. A comparative study of the antioxidant and ACE inhibitory activities of selected herbal extracts. Journal of Herbal Medicine 2020; 22: 100343

[43] Adam Y, Nasaruddin AA, Zairaini A, Arifah AK, Omar Fauzee MS, Zakaria ZA and Somchit MN. Diuretic activity of roots from *Carica papaya* and *Ananas comosus* L. International Journal of Pharmaceutical Sciences Review and Research 2013; 23(1): 163-167.

[44] Sarfaraz S, Sarwar G, Fatima W, Ramzan S, Amjah R, *et al*. Evaluation of diuretic potential of lemon juice and reconstituted lemon drink. World J. Pharm Res 2015; 4(7): 254-259.

[45] Eliza de Castromoreira M, Pereira G, Dias DF, Gontijo VS, Vilela FC, Isaac de Morares G, Guisti-Paiva, Monrique dos Santos M. Anti-inflammatory effect of aqueous extract of roasted and green *Coffae arabica L*. Journal of Functional Food 2013; 5(1): 466-474.

[46] Ardiansyah OY, Sarhirakawa H, Koseki T, Komai M. Novel effects of s single administration of ferulic acid on the regulation of BP and the hepatic lipid metabolism in stroke-prone spontaneously hypertensive rats. J Agric Food Chem 2008; 56: 2825-2830

[47] Patay EB, Fritea L, Antenescu A, and Dobjanschi L.*Coffae Arabica*: a plant with rich content in caffeine 2016. Doi: 10.5772/intechopen.68149

[48] Silvarolla M, Mazzafera P, Fazuoli L. A naturally decaffeinated *arabica Coffee*. Nature 2014; 429: 826

[49] Sharifi N, Souri E, Ziai SA, Amin G and Amanlou M. Discovery of new angiotensin-converting enzyme (ACE) inhibitors from medicinal plants to treat hypertension using an *in vitro* assay. DARU Journal of Pharmaceutical Sciences 2013; 21: 74.

[50] Ekpenyong CE, Daniel N, Akpan E. Phytochemistry and diuretic activity of *Cymbopogon citratus* leaf infusion in humans. Journal of Coastal Life Medicine 2014; 2(9): 704-713.

[51] Garcia R, Ferreira J, Costa G, Santos T. Evaluation of anti-inflammatory and analgesic activity of *Cymbopogon citratus in-vivo* polyphenols contribution. Research Journal of Medicinal Plants 2015; 9(1): 1-13.

[52] Ekpenyong CE, Akpan E, Nyoh A. Ethno-pharmacology, phytochemistry, and biological activities of *Cymbopogon citratus* (DC) Stapf extract. Chinese Journal of Natural Medicine 2015; 13(5): 321-337.

[53] Ali BH, Al Wabel, N, and Blunden G. Phytochemical, pharmacological and toxicological aspects of *Hibiscus sabdariffa* L.: a review. *Phytother Res* 2005; 19: 369-375.

[54] Herrera-Arellano A, Miranda-Sanchez J, Avila-Castro P, Herrera-Alvarez S, Jimenez-Ferrer JE, Zamilpa A, Roman Romus R, Ponce Monter H, Tottorielo J. Clinical effects produced by a standardized herbal medicinal product of Hibiscus *sabdariffa* on patients with hypertension. A randomized, double-blind, lisinopril-controlled clinical trial. *Planta Med* 2007; 73: 6–12.

[55] Alarcón-Alonso J, Zamilpa A, Aguilar FA, Herrera-Ruiz M, Tortoriello J and Jimenez-Ferrer E. Pharmacological characterization of the diuretic effect of *Hibiscus sabdariffa* Linn (Malvaceae) extract. *J Ethnopharmacol* 2012; 139: 751–756.

[56] Onuka AE, Emmanuel MP, Egbengu EE. Anti-inflammatory activity of methanolic extract of *Hibiscussabdariffa* in comparison with aspirin. The Pharma Innovation Journal 2014; 3(3): 42-47.

[57] Mea A, Sedagbande S, Abo KJ, Kahou BG. Diuretic activity of *Hibiscus sabdariffa* L in Wistar rats. International Journal of Pharmacology, Phytochemistry, and Ethnomedicine 2018; 9: 10-17.

[58] Omar ME. Anti-inflammatory, antinociceptive and gastric effect of Hypericum perforate in rats. The Scientific world journal 2005; 5: 580-595.

[59] Acuram LK and Hernandez C. Anti-hypertensive effect of *Moringa oleifera Lam*. Cogent Biology 2019; 5: 1596526

[60] Shenoy JP, Pal P, Shreb A, Gokul P. An evaluation of the diuretic activity of *Morinda citrifolia*(linn) Noni juice in normal rats. International journal of Pharmaceutical Sciences 2011; 3(2): 119-121.

[61] Zaoui A, Cherrah Y, Laccailler-Dubios MA, Setaff H, Amarouch H, and Hassar M. Diuretic and hypotensive effects of *Nigella sativa* in spontaneously hypertensive rats. Therapeutics 2000; 55(3): 379-382.

[62] Amin B, and Hasem Z. Black seed (*Nigella sativa*) and its active constituent-thymoquinone: an overview on the analgesic and anti-inflammatory effects. Planta Medica 2016; 82: 8-16.

[63] Persson IA, Dong L, Persson K. Effect of Panax ginseng extract (G115) on angiotensin-converting enzyme (ACE) activity and nitric oxide (NO) production. Journal of Ethno-pharmacology 2006; 105(3): 321-325.

[64] Han SY, Kim J, Kim E, Kim SH, Seo DB, Kim JH, Shin SS, Cho JY. AKT-targeted anti-inflammatory activity of *Panax ginseng* calyx ethanolic extract. Journal of Ginseng Research 2018; 42(4): 496-503.

[65] Jayshri T and Patil V. 3rd International conference and exhibition on Pharmacognosy, phytochemistry and natural products, Hyderabad, India October 2015; 26-28.

[66] Parasuraman S, Thing SG, Dhanaraj SA. Polyherbal formulation: concept of Ayurveda. Pharmocogn Rev 2014; 8(16): 73-80.

[67] Che CT, Wang ZJ, Chow MS, Lam CW. Herb-herb combination for therapeutic enhancement and advancement: theory, practice and future perspectives. Molecules 2013; 18(5): 5125-5141

[68] Vickers A and Zollman C. ABC of complementary herbal medicine. BMJ 1994; 319: 1050-1053.

[69] Ezuruike U, Prieto, JM. Assessment of potential Herb-Drug Interractions among Nigerian adults with type 2 diabetes. Front Pharmacol 2016; 7: 248. Doi:10:3389/fphav2016.00248.

[70] Yang Y, Islam MS, Wang J, Chen X. Traditional Chinese medicine in the treatment of patients infected with 2019 new corona virus (SARs-CoV2): a review. Int J Biol Sci 2020; 16(10): 1708-1717.

[71] Kahraman C, Aritulik ZC, Chanakya IT. The clinical

importance of herb-drug interaction and toxic 2020. DIO: 10.5772/intechopen.92040.

[72] Nugraha RV, Ridwansyab H, Ghozali M, Khairani AF, Atik N. G Traditional Herbal Medicine Candidates as complementary treatment for covid-19: A review of their mechanisms, pros and Con. Evidence-based complementary and Alternative medicine 2020, https://doi.org//10.1155/2020/2560645.

[73] Panyod S, Ho CT, Sheen LY. Dietary therapy and herbal medicine for Covid-19 preventive: Areview and perspective. Journal of Traditional and Complementans Medicine 2020; 10(4): 420-427.

[74] Tan BK, Vanitha J. Immunomodulatory and antimicrobial effects of some traditional Chinese medicinal herbs: a review. Curr Med Chem 2004; 11(11): 1428-1436.

[75] Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: a nested case-control study. *BMJ (Clinical Research Ed)* 2013; *346*: e8525.

[76] Oates T, Moochhala, S. Recognition and management of acute kidney injury. Available from www.prescriber.co.uk/article recognition-management -acute-kidney-injury 2017. (Accessed February 2020).

[77] Dreischutte T, Morales DR, Bell S, Guthrie B. Combination use of non-steroidal anti-inflammatory drugs with diuretic and/or renin-angiotensin system inhibitors in the community increase the risk of acute kidney injury. Kidney Int 2015; 88: 396-403.

[78] BPAC. Avoiding the triple whammy in primary care: ACE inhibitor/ARB + Duiretic + NSAIDs 2018. Available at www.bpac.org/2018/tripple-whammy.aspx. Accessed 07 October 2020.

Citation: **Christopher E. Ekpenyong, Ernest E. Akpan.** *Kidney Injury, Polyherbal Therapy and "Triple Whammy": Trends in Covid-19 Pandemic. Archives of Nephrology. 2020; 3(2): 38-48.*