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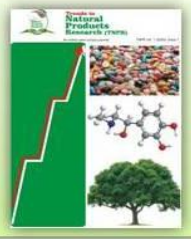

Pharmacological interactions involving drugs and four common medicinal plants used in Nigerian traditional medicine.

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Keywords: Medicinal plants, herb-drug interaction, conventional drugs, health professionals.

Abstract: Concomitant use of medicinal plants and conventional drugs may cause adverse events. Evidence available in literature indicates various mechanisms through which this can occur. By interacting with conventional medication, herbal remedies may precipitate manifestations of toxicity or in the other extreme, therapeutic failure. A good knowledge of the potential of commonly consumed herbal medicines to interact with prescription medicines, irrespective of the nature of evidence available, will equip health professionals in the practice. Apart from those demonstrated in significant number of human subjects, not all reported HDIs are clinically significant. As such more clinically relevant research in this area is necessary. Therefore, medicinal plants should be used concomitantly with conventional drugs with caution.

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DOI: 10.48245/tnpr-2734391.2021.2.212
Page No.: 109-114
Volume: 2, Issue 2, 2021
Trends in Natural Products Research

INTRODUCTION

According to the World Health Organization, herbal medicines are defined as 'finished, labelled medicinal products that contain as active ingredients aerial or underground parts of plants, or other plant material (juices, gums, fatty oils, essential oils, and any other substances of this Nature), or combinations thereof, whether in the crude state or as plant preparations.

Pharmaceutical dosage forms containing plant material combined with chemically defined active substances, including chemically defined, isolated constituents of plants, are not considered to be herbal medicines.

There is increased incidence of global use of medicinal plants which cuts across social and racial classes, both in undeveloped, developed and developing countries. The consumption rate may be higher in undeveloped and poor resource nations due to high level of poverty that impact adversely on the capacity to afford the cost of conventional drugs for the management and treatment of diverse disease conditions. High proportion of the world population currently uses medicinal herbs as complementary or alternative medicine (Fasinu, *et al.,* 2012*).* Furthermore, most chronic disease patients often resort to complementary and alternative medicines treatment albeit inappropriately to manage their disease conditions with the potential risks of herb-drug interaction (Shackh, *et al*., 2020). The necessity of polypharmacy in the management of most diseases increases the use of these products with serious risk of herbal-drug- interaction in patients.

In many countries herbal remedies are not subjected to strict regulation as they are promoted as natural and harmless (Homsy *et al*., 2004; Routledge, 2008). Hence, the increased use of herbal drugs without stringent control. Herbs however, are not completely devoid of adverse reactions. Serious adverse reactions have been associated with medicinal herbs (Efferth and Kaina.,2011; Patel *et al*., 2011). Evidences abound in literature of many different side effects to herbs (Efferth and Kaina, 2011; Izzo, 2012) including adverse events caused by herb-drug interactions (Izzo and Ernst, 2009).

Among rural dwellers and patients with chronic ailments, the concomitant use of medicinal plants and prescription medications is a common practice, with the attendant herb-drug interaction (Klepser *et al.*, 2000). Consumption of grape fruit juice has been reported to increase oral bioavailability of nifedipine, lovastatin, midazolam, terfenadines and cyclosporine (Wen and Gorycki, 2019).

While many of the interactions reported are of limited clinical significance and many herbal products such as Black cohosh, saw palmetto, Echinacea, Hawthorn and Valerian seem to expose patients to minor risk under conventional pharmacotherapy, a few herbs, notably St. John's wort, may provoke adverse events sufficiently serious to endanger the patients' health (Izzo, 2012). Herbal medicines contain a combination of pharmacologically active plant constituents that are claimed to exert synergistic effects (Ernst *et al*., 2006; Ernst *et al*., 2008; Wang et al., 2008). Most of these secondary metabolites are generated through the shikimate, acetate–malonate and acetate–mevalonate pathways (Wang *et al*., 2008). As herbal medicines are mixtures of more than one active ingredient, such combinations of many substances obviously will increase the likelihood of interactions taking place. In theory, there will be higher herb-drug interactions than drug-to-drug interactions, since synthetic drugs usually contain characterized single chemical entities.

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Mechanisms of Herb-Drug Interactions

The bases of interactions between drugs and medicinal plants are not different from that of drug-to-drug interactions principles. Several mechanisms of herb-drug-interactions have been proposed (Fasinu *et al*., 2012; Asher *et al*., 2017). Among these mechanisms include; pharmacokinetic and pharmacodynamic (Price *et al*., 2006; Ma *et al*., 2009), alteration in renal elimination ((Isnard et al., 2004; Brown, 2017), alteration in gastrointestinal functions (Fugh-Berman 2020), inhibition and induction of transport and efflux proteins (Marzolini *et al*, 2004; Degorter *et al*., 2012) and enzyme inhibition and induction (Roby *et al*., 2000; Yim *et al.*, 2004; Hu *et al*., 2005; Amacher *et al*., 2010; Hiratsuka, 2011; Taki *et al*., 2012).

Literature reports have shown that most pharmacokinetic interactions of herbs affect the blood concentration of different conventional medicines that are metabolized by phase I drug metabolizing enzyme system (cytochrome P450) and or by P-glycoprotein which influences drug absorption and elimination (Amacher, 2010; Izzo, 2012,). P-glycoprotein limits the cellular transport from the intestinal lumen into epithelial cells and enhances the excretion of drugs from hepatocytes and renal tubules into the adjacent luminal space. These pathways of interactions may be influenced by polymorphisms in the genes for CYP enzymes and P-glycoprotein (Tomlinson *et al*., 2008). The risk of pharmacokinetic drug interaction poses two major extreme challenges – pharmacotoxicity and treatment failure. The former can result from the inhibition of the metabolic enzymes responsible for the metabolism and clearance of the drugs while the latter may be the consequence of enzymatic induction leading to faster drug metabolism. This is in addition to the intrinsic pharmacodynamic

actions of the herbal products themselves which may include potentiating, additive, antagonism, or neutralization effects.

Other mechanisms of pharmacokinetic HDI have been identified and include the alteration in the gastrointestinal functions with consequent effects on drug absorption; induction and alteration of renal excretion of drugs and their metabolites (Isnard *et al*., 2004*)*.

Pharmacodynamics interactions though less studied may potentiate the pharmacological and or toxicological action of synthetic drugs (additive or synergetic) or may reduce the efficacy of synthetic drugs (antagonistic). Warfarin interactions are a classical example of pharmacodynamic interactions. Theoretically, increased anticoagulant effects could be expected when warfarin is combined with coumarin-containing herbs or with antiplatelet herbs. Conversely, vitamin K-containing herbs can antagonize the effect of warfarin (Izzo, 2012).

Herb-drug interactions involving the following commonly used herbs in Nigeria have been documented;

Aloe vera, Mill

Aloe vera (Liliaceae) is used in western countries as a laxative and for dermatological conditions (Capasso *et al*, 2003, Ernst *et al*, 2006). The potential medicinal benefits of *A. vera* has been documented (Sampeth-Kumar *et al.,* 2010). Its anti-bacteria (Fani and Kohanti, 2012), and anti-diabetic (Choi *et al.,* 2013) have also been reported. Among Nigerian traditional healers *Aloe vera* is commonly prescribed as an antibacterial, antiseptic, wound healing and anti-inflammatory agent. The gel is used by women to treat rashes and to beautify the skin. In traditional Chinese medicine, *A. vera* is mainly employed for inflammatory conditions, diabetes and hyperlipidaemia. Blood loss during surgery as a result of a possible interaction between *A. vera* and the anaesthetic sevoflurane has been reported (Lee *et al*, 2004). An additive effect on platelet function has been hypothesized but not proven since both sevoflurane and *A. vera* may inhibit platelet aggregation (Izzo, 2012).

Mentha piperita, L

Mentha piperita (Peppermint, Labiateae) leaves have a long history of use in digestive disorders (Ernst *et al*, 2008). The use of *Menthan* piperita by Nigerian traditional healers is frequent. Among conditions where peppermint is routinely employed include, chronic cough, chest pain, asthma, and constipation. Evidence suggests that enteric-coated peppermint oil may be effective in relieving some of the symptoms of irritable bowel syndrome (Weerts *et al*., 2021). Some clinical data suggest that peppermint might increase the levels of drugs metabolized by CYP3A4, such as felodipine (Dresser *et al*, 2002).

Zingiber officinale

Zingiber officinale (Ginger, Zingiberaceae) preparations are effective in attenuating nausea and vomiting during pregnancy and during the post-operative period (Ernst *et al*, 2008). In addition to its household use as spice, ginger is traditionally employed to treat fever, pain, malaria, cold and postpartum bleeding. Ginger has been reported to exhibit therapeutic benefits (Kauser, *et al.,* (2021). The anti-oxidant (Ahmed, *et al.,* 2008), anti-inflammatory (Grzama *et al.,* 2005), anti-cancer (Jeong, *et al.,* 2009) and anti-diabetic (Shidfar*, et al*., *2015)* potentials of *Z. officinale* have been documented. Ginger was reported to showed considerable antiplatelet effects in preclinical studies (Capasso *et al*, 2003) and this might explain the elevated international normalized ratio (INR) in a patient taking it concomitantly with the anticoagulant phenprocoumon (Krüth *et al*,2004). However, such an interaction has not been confirmed by a clinical trial (Jiang *et al*, 2005).

***Allium sativum,* L**.

Allium sativum (Garlic, Alliaceae) is the most popularly used and highly valued spice in Nigeria, and can be found in most of the traditional remedies. Garlic is employed alone or in combination with other herbs for the treatment of stomach pains, urinary tract infections, respiratory tract infections, bacterial and fungal infections, wounds, and asthma. In modern phytotherapy, it is used to treat hypercholesterolaemia and prevent arteriosclerosis although the clinical evidence is far from compelling (Ernst *et al*, 2006; Ernst *et al*, 2008). The therapeutic value of garlic is enormous (Fesseha and Goza, 2019). Some of the documented actions of gallic are, anti-microbial (Palaksha, *et al.,* 2010; Meriga, *et al.,* 2012), anti-cancer (Antony and Singh, 2011), anti-helminthic (Anthony, *et al.,* 2005), anti-inflammatory (Hodge, *et al.,*2002; Shih, *et al.,* 2010) and anti-oxidant (Banerjee, *et al.,* 2001; Bajpai., *et al.,* 2005) Garlic preparations include garlic powder standardized to contain 1.3 % alliin and 0.6 % allicin, garlic aged extract, which does not contain allicin but is high in water soluble phytochemicals, such as diallyl sulphides and garlic oil (Capasso *et al*, 2003). Two garlic preparations, namely garlic oil and garlic powder, have been evaluated for their potential to affect CYP enzymes in clinical trials. The results suggest that garlic oil may selectively inhibit CYP2E1, but not other CYP isoforms (such as CYP1A2, CYP3A4 or CYP2D6) and that garlic powder has no effect on CYP3A4 (Gurley *et al,*

2002; Markowitz *et al,*2003; Gurley *et al*, 2005; Jabbari *et al*, and Cox *et al*, 2006).
It has been shown that a 21-day garlic treatment(aged garlic extract) induces intestinal expression of P-glycoprotein without affecting intestinal or hepaticCYP34A in humans (Hajda *et al*, 2010).The most thoroughly studied garlic interactions with conventional drugs include interactions with the anticoagulant warfarin, which, in any case, have not been confirmed by controlled clinical trials or antiretroviral drugs (Laroche *et al*, 1998; Piscitelli *et al,* 2002; Gallicano *et al*, 2003; Pathak *et al*, 2003; Abdul *et al*, 2008; Berginc *et al*, 2010) Other irrelevant and/or poorly documented interactions include changes in paracetamol pharmacokinetics (Gwilt *et al*, 1994) and hypoglycaemia when combined with the antidiabetic drug chlorpropamide

CONCLUSION

The concomitant use of traditional medicines and orthodox drugs is prevalent in Nigeria, especially among the rural dwellers and patients suffering from chronic disease conditions that have not responded to orthodox drugs effectively. Four herbs - *Aloe vera, Mentha piperita, Zingiber officinale,* and *Allium sativum*-are commonly found in Nigerian traditional remedies. Evidence of herb-drug interactions with these herbs which may not be available to users have been documented. These herbs should be used with caution in combination with conventional drugs.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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CITATION: Akah PA and Nnamani ME (2021). Pharmacological interactions involving drugs and four common medicinal plants used in Nigerian traditional medicine. Trend Nat Prod Res 2(2). 109-114. DOI: 10.48245/tnpr-2734391.2021.2.212