





# Simultaneous Use of Herbal Medicines and Antihypertensive Drugs Among Hypertensive Patients in the Community: A Review

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**Abstract:** In various countries, approximately 80% of patients use herbal medicine, both in single form or in combination with antihypertensive drugs, for the treatment of hypertension. Therefore, this research summarized studies on the simultaneous use of herbal medicines and antihypertensive drugs among hypertensive patients in the community. A literature search was conducted on PubMed in April 2020, and the following keywords were used: “herbal medicines” and “antihypertensive patients.” In total, 15 of 263 articles were found to be eligible in the initial research. Results showed that studies were performed in different countries worldwide including America and those in Europe, Asia, and Africa between 1960 and 2020. The factors associated with the use of herbal medicines and antihypertensive drugs were age, gender, education level, income, and residence. Herbal medicines and antihypertensive drugs are simultaneously utilized primarily due to their safety and high efficacy. Herbal medicine is frequently recommended by friends or colleagues, herbalists, advertisements, and health workers. Garlic is the most common herbal medicine used along with antihypertensive drugs. The side effects of combination therapy with herbal medicines and prescription drugs for the management of antihypertension include shortness of breath and cough, ulcers, diarrhea, knee cramps, and abdominal discomfort. The lack of communication between patients and health care workers could cause an increase in the simultaneous use of herbal medicines and antihypertensive drugs. Therefore, effective communication among health care workers and appropriate care are important in preventing the side effects and other risks of combined therapy.

**Keywords:** combination use, herbal medicine, antihypertensive drug, hypertensive patients

## Introduction

Hypertension, or high blood pressure, is one of the common health problems worldwide. Its prevalence is high, and it is considered a major risk factor for cardiovascular diseases and other complications.<sup>1</sup> According to the World Health Organization, high blood pressure occurs when two consecutive measurements remain  $\geq 140/90$  mmHg. Approximately 30% of men and 50% of women aged 65–75 years present with hypertension. Moreover, 1.56 billion people are hypertensive worldwide. This value indicates a 60% increase in the prevalence of hypertension.<sup>2</sup>

Currently, approximately 75%–80% of the world’s population, including hypertensive patients, use herbal medicines due to the receptive nature of the body toward herbs, and the low incidence of side effects.<sup>3</sup> Several ethnobotany studies conducted in various parts of the world have shown that hundreds of plants can lower blood pressure.

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Therefore, they are used in the treatment of hypertension.<sup>4</sup> Approximately 47.5% of hypertensive patients simultaneously use herbal medicines and antihypertensive drugs.<sup>5</sup> In a study conducted in Jamaica, 79.5% of these patients also utilize this drug combination.<sup>6</sup>

Another article reported that 78 (19.5%) of 400 hypertensive patients simultaneously used herbal complementary therapy and conventional medicine.<sup>7</sup> The increasing use of this drug combination and its side effects caused a global health problem that should be addressed. Therefore, the safety of herbal medicine should be assessed to minimize unexpected risks.<sup>6</sup>

A systemic review of the prevalence of traditional drugs, time and effect of use, and reasons for use among hypertensive patients have been performed particularly in Sub-Saharan Africa.<sup>5</sup> In the study of Agbabiaka et al, herbal medicines and prescription drugs were simultaneously used. However, this review did not focus on hypertensive patients.<sup>8</sup> Meanwhile, Rahmawati and Bajorek conducted a study on self-medication using over-the-counter drugs and complementary alternative medicines among hypertensive patients. However, the use of herbal medicines was not specified.<sup>9</sup> Furthermore, no specific review was performed on patient criteria, sociodemographic characteristics, reasons for the simultaneous use of herbal medicines and antihypertension drugs, herbal names, drugs used, and perceived side effects of combination therapy. Therefore, this article aimed to discuss the simultaneous use of herbal medicines and antihypertensive drugs among hypertensive patients in the community. Moreover, the sociodemographic characteristics and factors correlated with this combination therapy, considered as evidence-based information, and its unexpected risks were discussed.

## Literature Search

A literature search was conducted on PubMed in April 2020 using keywords such as “herbal medicines” and “hypertensive patients.” The detailed keywords were as follows: (“plants, medicinal”[MeSH Terms] OR “plants”[All Fields]) AND (“medicinal”[All Fields] OR “medicinal plants”[All Fields] OR “herbal”[All Fields]) AND (“medicines”[All Fields] OR “herbal medicines”[All Fields]) AND (“hypertense”[All Fields] OR “hypertension”[MeSH Terms] OR “hypertension”[All Fields] OR “hypertension s”[All Fields] OR “hypertensions”[All Fields] OR “hypertensive”[All Fields] OR “hypertensive s”[All Fields] OR “hypertensives”[All Fields]) AND (“patients”[All Fields] OR “patients”[MeSH Terms] OR “patients”[All Fields] OR “patient”[All Fields]

OR “patients s”[All Fields]). This study included research studies, articles written in English, and survey research on the combined use of herbal medicines and prescribed drugs among hypertensive patients. The flow chart of the literature is depicted in Figure 1.

## Use of Herbal Medicines Among Hypertensive Patients

Table 1 shows the summary of 15 cross-sectional studies on the use of herbal medicines among hypertensive patients. These studies had been carried out in various countries including America and those in Europe, Asia, and Africa between 1960 and 2020. In total, 7302 hypertensive patients participated in these studies. Furthermore, 3714 hypertensive patients used herbal medicines, and 262 simultaneously used herbal medicines and antihypertensive drugs. Fifteen research articles discussed the proportion of patients who used a combination of drugs, and six articles showed the number of hypertensive patients who received combination therapy.

## Sociodemographic Characteristics of Hypertensive Patients Who Simultaneously Used Herbal Medicines and Antihypertensive Drugs

Table 2 depicts the sociodemographic characteristics of hypertensive patients who simultaneously used herbal

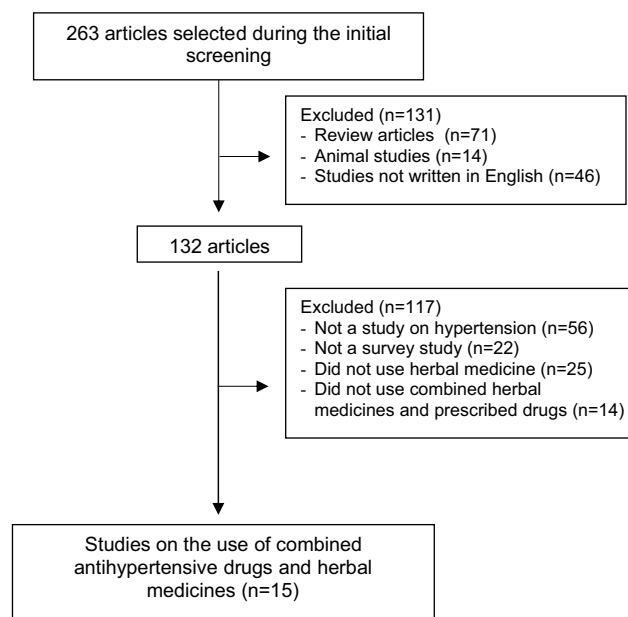


Figure 1 Flowchart of literature search.

Table 1 Use of Herbal Medicines Among Hypertensive Patients Between 1960 and 2020

No.	Country	Number of Participants	Number of Hypertensive Patients	Number of Hypertensive Patients Who Used Herbal Medicine	Number of Patients Who Simultaneously Used Herbal Medicines and Antihypertensive Drugs	References
1	Australia	n=260	n=260	n=148	Not indicated	James <sup>10</sup>
2	Palestine	n=4575	n=3921	n=2436	Not indicated	Ali Shtayeh <sup>11</sup>
3	Jordan	n=378	n=32	n=32	Not indicated	El-Dahiyat <sup>12</sup>
4	Turkey	n=343	n=184	n=168	Not indicated	Aykan dan Aykan <sup>13</sup>
5	Iran	n=612	n=612	n=169	Not indicated	Tajadini <sup>14</sup>
6	Africa	n=135	n=135	n=28	Not indicated	Hughes <sup>5</sup>
7	Thailand	n=1374	n=838	n=272	Not indicated	Peltzer and Pengpid <sup>16</sup>
8	Iraq	n=20	n=20	n=11	Not indicated	Ibrahim <sup>17</sup>
9	Nigeria	n=225	n=225	n=35	Not indicated	Amira and Okubadejo <sup>18</sup>
10	South Africa	n=456	n=124	n=66	37.1% (n=46)	Hughes <sup>19</sup>
11	Trinidad	n=265	n=74	n=53	30.6% (n=81)	Clement <sup>20</sup>
12	Jamaica	n=270	n=42	n=42	10% (n=27)	Picking
13	Tanzania	n=213	n=213	n=69	22.1% (n=47)	Liwa <sup>22</sup>
14	West Africa	n=316	n=142	n=65	6.2% (n=4)	Diallo <sup>23</sup>
15	Nigeria	n=480	n=480	n=120	47.50% (n=57)	Olisa and Oyelola <sup>24</sup>
		(n=9466)	(n=7302)	(n=3714)	(n=262)	

Table 2 Sociodemographic Characteristics of Hypertensive Patients Who Use Herbal Medicines Combined with Antihypertensive Drugs

No.	Number of Hypertensive Patients	Number of Hypertensive Patients Who Used Herbal Medicines	Number of Patients Who Simultaneously Used Herbal Medicines and Antihypertensive Drugs	Gender	Age	Education Level	Occupation	Income	Residence	References
1	n=124	n=66	37.1% (n=46)	M: 20.3% F: 79.7%	56 years old on average	<ul style="list-style-type: none"> <li>None or primary: 37.4%</li> <li>Secondary: 54.5%</li> <li>Tertiary or others: 8.1%</li> </ul>	<ul style="list-style-type: none"> <li>Employed (19.7%)</li> <li>Unemployed (80.3%)</li> </ul>	<ul style="list-style-type: none"> <li>0–1999 rand: 75%</li> <li>2000–5000 rand: 21.0%</li> <li>5000+ rand: 4%</li> </ul>	Urban	Hughes <sup>19</sup>
2	n=74	n=53	30.6% (n=81)	Not indicated	–	–	–	–	–	Clement <sup>20</sup>
3	n=42	n=42	10% (n=27)	Not indicated	–	–	–	–	–	Picking <sup>21</sup>
4	n=213	n=69	22.1% (n=47)	M: 40.4% F: 59.6%	<ul style="list-style-type: none"> <li>≤45 years old: 21.7%</li> <li>46–55 years old: 30.0%</li> <li>56–65 years old: 20.1%</li> <li>&gt;65 years old: 27.1%</li> </ul>	<ul style="list-style-type: none"> <li>Did not complete primary school: 36.2%</li> <li>Completed primary school: 22.3%</li> <li>Completed secondary school: 11.8%</li> </ul>	<ul style="list-style-type: none"> <li>Farmers (32%)</li> <li>Small scale business owners (33.3%)</li> <li>Professionals, businessman or businesswoman, or students (11.1%)</li> </ul>	–	–	Liwa <sup>2</sup>
5	n=142	n=65	6.2% (n=4)	M: 26.15% F: 73.84%	<ul style="list-style-type: none"> <li>45–54 years old: 58.5%</li> </ul>	–	–	–	Urban	Diallo <sup>23</sup>

6	n=480	n=120	47,50% (n=57)	Not indicated	<ul style="list-style-type: none"> <li>● 60–69 years old: 33.33%</li> <li>● 70–79 years old: 41.67%</li> </ul>	<ul style="list-style-type: none"> <li>● Without formal education: 42.42%</li> <li>● Primary education: 41.67%</li> </ul>	-	-	-	Olisa and Oyelola <sup>24</sup>
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Abbreviations: n, number of patients; M, male; F, female.

medicines and antihypertensive drugs in six articles. These characteristics include gender, age, education level, occupation, income, and residence.

In total, three articles showed that the number of female patients using combined herbal medicines and antihypertensive drugs was higher than that of male patients.<sup>19,22,23</sup> Two studies in Africa revealed that the number of female hypertensive patients who used herbal medicines for treating hypertension was higher than that of male hypertensive patients (79.7% and 73.84%, respectively).<sup>19,23</sup> In Tanzania, the number of female patients (59.6%) who simultaneously used herbal medicines and antihypertensive drugs for the management of hypertension was higher than that of male patients (40.4%).<sup>22</sup> This finding was in accordance with that of a research conducted in Turkey that showed that the number of female patients (84.1%) was higher than that of male patients (15.9%).<sup>25</sup> Clement et al conducted a study in Trinidad and results showed that the number of female patients (73.20%) who used herbal medicine for the treatment of hypertension was higher than that of male patients (26.8%).<sup>20</sup> Therefore, based on the gender criteria of the three articles in this review, female patients were the most common users of combined herbal medicines and antihypertensive drugs.

In total, four articles discussed the age of hypertensive patients who used herbal medicines. Studies from Diallo revealed that approximately 58.5% of herbal users in Guinea City, Africa, were aged 45–55 years.<sup>23</sup> Meanwhile, Liwa et al showed that approximately 27.1% of users in Tanzania were aged >65 years.<sup>22</sup> Olisa et al performed a study in Nigeria. Results showed that approximately 41.67% of herbal users were aged 70–79 years.<sup>24</sup> Furthermore, a research conducted in South Africa showed that the users of herbal medicine were aged 49–64 years.<sup>19</sup> On the basis of these studies, the use of combined herbal medications and hypertensive drugs was found to be correlated with age.

Furthermore, three articles reported on the educational levels of herbal users. Hughes et al revealed that approximately 54.5% of participants had secondary education.<sup>19</sup> Liwa et al showed that 36.2% of patients did not graduate from elementary school; 22.3% and 11.1% completed primary and secondary schools, respectively; and 42.42% did not obtain any education.<sup>22</sup> Meanwhile, Olisa and Oyelola revealed that 42.42% of herbal users had no formal education.<sup>24</sup> This result was in accordance with that of the study of Aykan that showed that 57.1% of people in

Turkey had a low educational level.<sup>13</sup> However, this result was different from that of the study of Soner, which showed that 48.8% of herbal users were women with high educational levels and family incomes.<sup>26</sup>

In addition, the simultaneous use of herbal medicines and antihypertensive drugs was found to be correlated with occupational status, as observed in the two articles.<sup>19,22</sup> Hughes et al showed that the utilization of combined herbal medicines and prescribed drugs was commonly observed in unemployed patients (80.3%), and approximately 19.7% of patients were workers or employees.<sup>19</sup> Meanwhile, Liwa et al revealed that combination treatment was frequently observed in patients with small businesses (33.3%), farmers (32.1%), and professionals and entrepreneurs (11.1%).<sup>22</sup>

In terms of residence, two articles showed that research was conducted in an urban area in West and South Africa.<sup>19,23</sup> However, Picking et al revealed that the use of herbal medicines was more commonly observed in hypertensive patients (21.8%) living in rural areas than in those (42.42%) living in urban areas.<sup>21</sup>

## Factors Correlated with the Simultaneous Use of Herbal Medicines and Antihypertensive Drugs

Table 3 presents the factors correlated with the simultaneous use of herbal medicines and antihypertensive drugs. These include the number of patients, reasons for use, informants, names or types of herbal medicines, methods of obtaining and using these medicines, type/name of hypertension drugs, and perceived side effects. Of the 15 research articles, only 6 discussed these factors.<sup>19–24</sup>

## Reasons for the Simultaneous Use of Herbal Medicines and Antihypertensive Drugs

The reasons for using combined herbal medicines and antihypertensive drugs varied in 11.1–23.08% of patients. That is, conventional medicine was more expensive than herbal medicine.<sup>19,21,24</sup> Approximately 31.9% of patients believed that traditional medicine was effective on the basis of their social and cultural beliefs (20.19–33.3%) and family history (48.8%).<sup>5,19,24</sup> Tajadini showed that herbal medicines were used as adjunctive therapy for lowering blood pressure.<sup>14</sup> Meanwhile, approximately

8–70.4% of patients claimed that herbal medicines were highly effective and did not cause problems when used concurrently with antihypertensive drugs.<sup>20–22</sup> This result was similar to that of the study of Delgoda et al that showed that the reason for the concurrent use of herbal medicines and prescribed drugs was attributed to hereditary beliefs.<sup>6</sup>

## Individuals Who Recommend the Simultaneous Use of Herbal Medicines and Antihypertensive Drugs

Hughes et al revealed that hypertensive patients used herbal remedies based on recommendations by family (58.7%), friends or colleagues (18.1%), advertisements (2.6%), and herbalists (6.9%). Meanwhile, only 1.7% of participants used herbal medicines according to the recommendation of health care workers.<sup>19</sup> Liwa et al showed that approximately 1.5% of recommendations were from herbalists.<sup>5</sup> Olisa and Oyelola explained that the use of herbal medicines among hypertensive patients was recommended by sales representatives.<sup>24</sup> Furthermore, in Ethiopia, it was widely recommended by herbalists to 37.8% of users who were not satisfied with the conventional therapy.<sup>27</sup> Some studies showed that the increasing use of herbal medicine for the treatment of hypertension was attributed to the assumption that herbal medicines do not have several side effects as compared with prescription drugs or chemicals. Moreover, the use of herbal medicine was a hereditary culture.<sup>19,22,23</sup> Erku showed that 70.2% of patients did not inform health workers about the use of herbal medicine, and they did have sufficient knowledge regarding such therapy.<sup>27</sup> They refused to inform health workers, believing that it was unnecessary (53.6%), and some were afraid that their physicians would be angry or upset (7.1%). Moreover, approximately 28.6% were not assessed regarding the use of this therapy.<sup>28</sup> A research conducted in Ghana showed that approximately 70% of hypertensive patients who use herbal medicine did not inform health workers due to fear and lack of information regarding herbal treatments.<sup>7</sup>

## Types of Herbal Medicines and Antihypertensive Drugs

Garlic has been used as a herbal medicine for hypertension and was used in four studies.<sup>20–22,24</sup> According to the research conducted by Liwa et al, 83.2% of patients were not familiar with the name of the herbal medicine.

**Table 3** Factors Correlated with the Simultaneous Usage of Herbal Medicines and Antihypertensive Drugs

No.	Reasons for Usage	Informants	Name of Herbal Medicines	Source	Consumption Process	Antihypertensive Drugs	Perceived Side Effects	References
1	<ul style="list-style-type: none"> <li>Assuming conventional drugs was unsuccessful (31.37%)</li> <li>Conventional medicine was more expensive (23.08%)</li> <li>Sociocultural (community) habits (20.19%)</li> <li>Difficult access to health facilities (19.23%)</li> <li>Safety issues associated with conventional medicine (9.26%)</li> <li>Lack of attention from hospital staff (6.73%)</li> </ul>	Salesman and friend	<ul style="list-style-type: none"> <li><i>Azadirachta indica</i> (12.50%)</li> <li><i>Allium sativum (garlic)</i> (9.62%)</li> <li><i>Aloe vera</i> (7.69%)</li> <li><i>Tamarindus indica</i> (7.69%)</li> </ul>	<ul style="list-style-type: none"> <li>Market (26.52%)</li> <li>Friends (20.56%)</li> <li>Traditional medicine stores (19.79%)</li> <li>Pharmacists (9.09%)</li> </ul>	<ul style="list-style-type: none"> <li>Infusing the herbal material using a different solvent as vehicles, which include water, lime juice, and corn pap</li> <li>Steam inhalation</li> </ul>	-	Diarrhea, stomach ulcers, abdominal discomfort, leg cramps, shortness of breath and cough	Olisa and Oyelola <sup>24</sup>
2	<ul style="list-style-type: none"> <li>Family history (48.8%)</li> <li>Cultural beliefs (33.3%)</li> <li>Low cost (16.3%)</li> <li>Ease of obtaining herbal medicine (12.2%)</li> <li>Positive recommendation (22.8%)</li> <li>Maintaining health condition (32.5%)</li> <li>Drugs for specific diseases (13.0%)</li> </ul>	<ul style="list-style-type: none"> <li>Friends or colleagues (18.1%)</li> <li>Partners (6.0%)</li> <li>Family (57.8%)</li> <li>Traditional practitioners (6.9%)</li> <li>Advertisements (2.6%)</li> <li>Health care providers (1.7%)</li> </ul>	-	<ul style="list-style-type: none"> <li>Market (39.5%)</li> <li>Traditional practitioners (26.6%)</li> <li>Personal harvest (21%)</li> </ul>	<ul style="list-style-type: none"> <li>Tea (83.9%)</li> <li>Powder (9.3%)</li> <li>Extract (10.2%)</li> <li>Tablet (2.5%)</li> <li>Decoction (6.8%)</li> </ul>	-	-	Hughes. <sup>19</sup>

(Continued)

Table 3 (Continued).

No.	Reasons for Usage	Informants	Name of Herbal Medicines	Source	Consumption Process	Antihypertensive Drugs	Perceived Side Effects	References
3	<ul style="list-style-type: none"> <li>● Belief in traditional medicines (31.9%)</li> <li>● Convinced by others (17.4%)</li> <li>● Pressure from family or spouse (10.2%)</li> <li>● Indifference among hospital staff (7.3%)</li> </ul>	Traditional medications (15%)	<ul style="list-style-type: none"> <li>● Garlic, ginger, honey, carrots, avocado seeds, bit roots, wood charcoal, papaya seeds, lemons, onions, and aloe vera</li> </ul>	-	-	-	-	Liwa. <sup>22</sup>
4	Combination of herbal medicines and drugs works effectively (70.4%)	-	<i>Allium sativum</i> (garlic) (12.4%)	<ul style="list-style-type: none"> <li>● Garden/backyard (79.2%)</li> <li>● Market (7.5%)</li> </ul>	-	-	-	Clement. <sup>20</sup>
5	<ul style="list-style-type: none"> <li>● Simultaneous use of drugs works effectively (12.5%)</li> <li>● Prescription of a single medicine did not work effectively (5.5%)</li> <li>● Prescription of an expensive drug (1.1%)</li> <li>● Many side effects from prescribed drugs (8.3%)</li> <li>● Simultaneous use of herbal medicines and drugs was safe (8%)</li> <li>● Do not take prescription drugs for the same condition (48.6%)</li> </ul>	-	<ul style="list-style-type: none"> <li>● <i>Momordica charantia</i> L. (42.2%)</li> <li>● <i>Allium sativum</i> (garlic) L. (12.6%)</li> <li>● <i>Morinda citrifolia</i> Hunter (7.8%)</li> <li>● <i>Zingiber officinale</i> Roscoe (13.7%)</li> <li>● <i>Eupatorium odoratum</i> L. (22.6%)</li> </ul>	-	-	<ul style="list-style-type: none"> <li>● HCT (13.9%)</li> <li>● Captopril (2.8%)</li> <li>● Atenolol (4.2%)</li> <li>● Enalapril (8.2%)</li> <li>● Hydralazine (4.2%)</li> <li>● Nifedipine (4.2%)</li> <li>● Furosemide (4.2%)</li> <li>● Carvedilol (2.8%)</li> <li>● Bendroflumethiazide reserpine (2.8%)</li> </ul>	-	Picking. <sup>21</sup>
6	Culture, sociodemographic characteristics, and high cost of modern therapy	-	<ul style="list-style-type: none"> <li>● <i>Hymenocardia acida</i></li> <li>● <i>Uapaca togoensis</i></li> <li>● <i>Hibiscus sabdariffa</i></li> </ul>	Market (54.8%) and harvest themselves (45.1%)	Decoction (73.3%) and infusion (26.6%)	-	Diuretic	Diallo. <sup>23</sup>

Abbreviation: HCT, hydrochlorothiazide.



Meanwhile, 16% were cognizant, and 13.0% used more than one herbal ingredient, one of which was garlic (29.72%).<sup>22</sup> This study showed that in addition to *Azadirachta indica*, garlic (9.62%) is also a herbal medicine used by hypertensive patients in Nigeria.<sup>24</sup> Meanwhile, the research conducted in Trinidad showed that garlic was the most widely used herb for the management of hypertension, and approximately 48.3% of patients used combined garlic and antihypertensive drugs.<sup>20</sup> These results were in accordance with those of the study of Aykan. This research showed that 71.2% of patients with cardiovascular diseases in Turkey used garlic, and 51.9% often took both garlic and antihypertensive drugs (beta [ $\beta$ ]-blocker).<sup>13</sup>

Garlic had several benefits in the treatment of cardiovascular diseases. These include lowering blood pressure, and the bioactive component of garlic had an antioxidant effect that can induce smooth muscle cell relaxation and vasodilation and lower blood pressure.<sup>22,29</sup> Picking et al showed that garlic is often used simultaneously with an antihypertensive drug, particularly hydrochlorothiazide (HCT), among hypertensive patients in Jamaica. Moreover, it is utilized simultaneously with captopril, hydralazine, nifedipine, and reserpine, in addition to HCT and  $\beta$ -blockers, and pear and breadfruit leaves.<sup>21</sup>

In addition to garlic, other types of herbal medicine are used. These include *Aloe vera* (7.69%), *Tamarindus indica* (7.69%), and *Azadirachta indica* (12.50%).<sup>24</sup> Some herbs used by hypertensive patients were *Momordica charantia* L. (42.2%), *Morinda citrifolia* Hunter (7.8%), *Zingiber officinale* Roscoe (13.75%), and *Eupatorium odoratum* L (22.6%).<sup>21</sup> Meanwhile, hypertensive patients in the urban area of Guinean in Belgium often use *Hymenocardia acida* leaves, *Uapaca togoensis* bark, and *Hibiscus sabdariffa*.<sup>23</sup>

The antihypertensive drugs commonly used in combination with herbal medicines include hydrochlorothiazide (13.9%), enalapril (8.3%), atenolol (4.2%), nifedipine (4.2%), hydralazine (4.2%), and captopril (2.8%).<sup>21</sup> Meanwhile, on the basis of research conducted in Turkey, the antihypertensive drugs often used in combination with herbal medicines include angiotensin-converting enzyme inhibitors (23.9%), angiotensin II receptor blockers (14.9%),  $\beta$ -blockers (51.9%), and calcium channel blockers (15.7%).<sup>13</sup>

## Source and Use of Herbal Medicine

The various methods used for obtaining herbal ingredients include independent planting; buying from shops, markets,

and supermarkets; and prescription from healthcare providers. However, most patients obtained herbal medicine from market purchases. Clement et al showed that herbal users in Trinidad obtained herbal medicine from their gardens or backyards (79.2%) and from markets (7.5%).<sup>20</sup> Meanwhile, a research conducted in Nigeria revealed that patients obtained herbal medicine from the market (26.52%), friends (20.56%), traditional medication stores (19.79%), and pharmacists (9.09%).<sup>24</sup> Approximately 54.8% of hypertensive patients in Guinean, Belgium, purchased herbal medicines from the market, and approximately 45.1% of patients harvested herbal medicines themselves.<sup>23</sup> Meanwhile, hypertensive patients in an urban South African community obtained herbal medicines from the market (39.5%), traditional practitioners (26.6%), and personal harvests (21%).<sup>19</sup> Finally, herbal ingredients were processed by infusing herbal materials using different solvents as vehicles, which include water, lime juice, and corn pap.<sup>24</sup> Herbal medicine is prepared as a decoction (73.3%) or an infusion (26.6%) using water.<sup>23</sup> Hypertensive patients take herbal medicines in the form of tea (83.9%), powder (9.3%), and extract (10.2%).<sup>19</sup>

## Herbal Medicine-Antihypertensive Drug Interaction

Herbal-drug interactions become clinically significant when considerable changes occur in the pharmacokinetic parameters of drugs that are taken with herbal medicine. The interactions often occur as a result of changes in drug metabolic activity and protein transport, especially cytochrome P450 and P-glycoprotein isoenzymes, which can be increased or inhibited by synthetic or herbal drugs.<sup>30,31</sup> Pharmacodynamic interactions can be additive (or synergistic) when herbal medicine potentiates the pharmacological or toxicological effects of synthetic drugs; for example, interactions between warfarin and the antiplatelet herbal medicine may enhance the anticoagulant effect of warfarin.<sup>32</sup>

Some examples of interactions between herbal medicine and antihypertensive drugs are as follows: amlodipine with ginkgo leaf tablets increased the  $T_{max}$ ,  $C_{max}$ ,  $t_{1/2}$ , and AUC of amlodipine, so ginkgo leaf tablets were suspected to change the pharmacokinetic parameters of amlodipine through modulation of the CYP3A4 enzyme metabolism.<sup>33</sup> Simultaneous use of Rosella and HCT can increase urine volume, decrease urine pH, and

concentrations of sodium, bicarbonate, and chloride ions. In addition, the use of rosella with HCT can increase and extend the Cmax, AUC, and volume distribution of HCT.<sup>34</sup> The use of propranolol and *Eurycoma longifolia* simultaneously can affect the propranolol absorption process, whereas *Eurycoma longifolia* induces the transport of P-glycoprotein (P-gp) waste, thereby increasing the extrusion of propranolol from epithelial cells into the intestinal lumen.<sup>35</sup> Meanwhile, the effects of breadfruit leaf and peperomia pellucida extracts on the activity of the CYP3A4 and CYP2D6 enzymes show that the two extracts do not cause significant side effects when consumed together with other medications that depend on CYP3A4 and CYP2D6 metabolisms.<sup>36,37</sup>

In addition, interactions that affect drug absorption may involve active transporters located in the intestinal membrane.<sup>38</sup> Intestinal metabolism plays an important role in drug bioavailability and clinical efficacy. Induction of this metabolic enzyme by xenobiotics can decrease the amount of drug absorbed, which leads to a loss of clinical efficacy. On the other hand, inhibition of intestinal metabolism increases the amount of drug available, increasing the possibility of toxicity and adverse drug reactions.<sup>39</sup> For example, when grapefruit juice is used simultaneously with felodipine or 1,4-dihydropyridine calcium antagonists, it can inhibit intestinal CYP3A4 and increase felodipine bioavailability, and inhibition of intestinal metabolism can increase the amount of drugs in the body, which can lead to toxicity and adverse drug reactions.<sup>39,40</sup> Another study suggested simultaneous use of peppermint oil capsules with felodipine can increase the bioavailability of felodipine and cause side effects such as headache, dizziness, and flushing.<sup>41</sup> Furthermore, the use of antihypertensive drugs can also have an antagonistic effect when used together with herbs with antihypertensive activity, causing vasoconstriction, fluid retention, and potential vasodilation.<sup>42</sup>

## Perceived Side Effects

The simultaneous use of herbal medicines and antihypertensive drugs caused unexpected side effects. As shown in the study of Aykan, approximately 6.7% of patients in Turkey experienced side effects.<sup>13</sup> The research conducted by Olisa and Oyelola revealed that in Nigeria, 21.04% of patients presented with side effects such as ulcers (3.51%), knee cramps (3.51%), shortness of breath and cough (3.51%), skin reactions (3.51%), erectile dysfunction (1.75%), diarrhea (1.75%), gastroenteritis (1.75%), and

abdominal discomfort (1.75%).<sup>24</sup> The patient believes that these side effects are due to the use of herbal medicine; these side effects were attenuated after the use of herbal medicine was stopped.<sup>24</sup> This result was quite similar to that of the research of Clement et al that showed that 6% of hypertensive patients using combination therapy in Trinidad experienced side effects.<sup>20</sup> In addition, other studies showed that this combination therapy increased the risk of diuresis, hypotension, and hypokalemia.<sup>43</sup>

According to the number of users and its side effects, special attention from health workers was required to address these issues. Meanwhile, the lack of communication between patients and doctors or other health care workers was the most common obstacle observed in all studies on herbal usage, both in singular and combined form.

## Conclusion

Herbal medicines and antihypertensive drugs were simultaneously used by 262 of 7302 hypertensive participants in this study. The frequent usage was found to be influenced by the sociodemographic characteristics, such as gender, age, education level, occupation, and residence. Herbal medicines and antihypertensive drugs were primarily used due to their safety and high efficacy. In this case, garlic was the most commonly used herbal medicine. Meanwhile,  $\beta$ -blocker is a class of antihypertensive drug often used simultaneously with herbal medicines. The side effects of combined herbal medicines and prescription drugs among hypertensive patients included shortness of breath and cough, ulcers, diarrhea, knee cramps, and abdominal discomfort. The factors associated with the increased usage of combined herbal medicines and drugs included perceived fear and lack of initiative from doctors and health workers. Effective communication among health care workers and appropriate care were required to prevent the side effects and other risks of combination therapy.

## Disclosure

The authors report no conflicts of interest in this work.

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