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Antioxidant, anti-inflammatory and antidiabetic activities of the combination of *Curcuma longa* (Zingiberaceae), *Aframomum melegueta* (Zingiberaceae) and *Piper guineensis* (Piperaceae) compared to plants alone

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ABSTRACT

Introduction

Diabetes mellitus is a group of diseases characterized by chronic hyperglycemia resulting from a disturbance in insulin secretion, function, or both. It is currently one of the major public health problems.

Purpose

The aim of this study was to quantify secondary metabolites, evaluate the biological activities of individual plants, and assess the combination's antioxidant, anti-inflammatory, and antidiabetic activities compared to the plants used individually.

Methods

To conduct this study, we examined the qualitative and quantitative composition of some metabolites using conventional methods. We assessed the antioxidant activities *in vitro* using DPPH• and ABTS• radicals. The antidiabetic activity was evaluated using the glucose oxidase method, while the anti-inflammatory activity was determined *in vitro* using the protein denaturation method (albumin).

Results

Our findings revealed that the CAP combination contained all the investigated metabolites, and the concentrations of polyphenols, flavonoids, and tannins were higher than those of the individual plants. The anti-inflammatory and antidiabetic activities of CAP were superior for both extracts, although the antioxidant activity of CAP was lower compared to *C. longa* and *A. melegueta* for organic extracts on the ABTS• radical.

Conclusion

The combination of these plants could be a prudent choice as part of a strategy to combat diabetes, particularly through herbal medicine.

INTRODUCTION

Diabetes mellitus is a group of diseases characterized by chronic hyperglycemia resulting from a disturbance of insulin secretion, function, or both (Darenska et al., 2021). It is accompanied by damage, dysfunction, and failure of certain organs, including the brain, kidneys, heart, and eyes (Berbundi et al., 2020). It represents a major public health problem.

According to the International Diabetes Federation (IDF, 2019), 463 million people were diagnosed with diabetes worldwide in 2019. In the Democratic Republic of Congo (DRC), the prevalence of diabetes, reported in a few fragmentary studies, varies between 3.5% and 14% of the population (Matulewicz et al., 2016). In 2016, approximately 23,000 deaths were attributed to diabetes or hyperglycemia (World Health Organization [WHO], 2019). The development and implementation of products capable of treating diabetes and its complications are of great importance.

Diabetes is linked to oxidative stress (Zhang et al., 2020) and chronic inflammation (Gloss & Olefsky, 2012). Currently, it is established that oxidative stress and the inflammatory response play a central role in the pathophysiology of diabetes, especially type 2 diabetes (Azizi et al., 2023). They impair insulin sensitivity and damage the β cells of the pancreas (Lontchi-Yimagou et al., 2013; Onyango, 2018; Berbundi et al., 2020).

Conventional antidiabetic drugs are effective despite their side effects. On the other hand, plants offer an alternative and promising source of therapeutic agents without significant side effects (Salehi et al., 2019). A meta-analysis demonstrated that treatments derived from hypoglycemic plants, compared to certain drugs, significantly improve oxidative stress, inflammation, total antioxidant capacity, and the activity of antioxidant enzymes (Azizi et al., 2023). The species *Curcuma longa* (*C. longa*), *Aframomum melegueta* (*A. melegueta*), and *Piper guineensis* (*P. guineensis*) exhibit proven antioxidant, anti-inflammatory, and antidiabetic effects (Mohammed et al., 2017; Omoba et al., 2019; Marchant et al., 2022). The presence of these activities is attributed to the combinatorial and concentrated action of their biologically active compound profiles (Salehi et al., 2019).

The aim of this study was to quantify secondary metabolites, evaluate the biological activities of individual plants, and assess the combination's antioxidant, anti-inflammatory, and antidiabetic activities compared to the plants used individually.

METHODS

Plant Material, Harvesting, and Packaging of Samples

We used the rhizome of *Curcuma longa* (*C. longa*) as plant material (Corsier-Baland, 980), *Aframomum melegueta* (*A. melegueta*) seeds (Pauwels, 4401), and the fruits of *Piper guineensis* (*P. guineensis*) (Devred, 719, 943). The plants were identified at the Herbarium of the National Institute of Agronomic Study and Research (INERA) of the Faculty of Sciences, University of Kinshasa, by Professor Blaise Bikandu. The samples of *A. melegueta* and *C. longa* were collected at the Batéké Plateau, while the seeds of *P. guineensis* were obtained from the province of Kwilu, in the Kipuka sector, Koko village, Bulungu territory.

Figure 1:
Plant Material, Harvesting, and Packaging of Samples

Sample Preparation

All samples (organs) were dried at laboratory temperature away from sunlight (*A. melegueta* and *P. guineensis* seeds) and in an oven (Melag Nurfur Wechselstrom) at 30 °C for

10 days for *C. longa* rhizomes (400 g), previously cut into small pieces. After drying, the different organs were ground using an electric grinder (IKA MF10 basic).

The mixture, based on the powders of *C. longa* rhizomes, *A. melegueta* seeds, and *P. guineensis* fruits, was prepared in the proportion of 5:2.5:2.5 grams or (50:25:25%) respectively, corresponding to traditional practitioners' mixtures. Additionally, we added 100 mL of solvent (80% methanol) for organic extracts and 100 mL of distilled water for aqueous extracts for 24 hours. The macerates obtained were filtered using Whatman paper No. 1, and the filtrates were placed in the oven to evaporate the solvent, yielding the dry extract for biological activities.

Phytochemical Screening

Preliminary Phytochemical Screening

Preliminary phytochemical screening was performed using color and precipitation reactions by adding specific reagents, following the method described by Harborne (1998), as cited by Nyamangombe et al. (2023).

Extraction of Active Ingredient(s)

The extraction of active ingredients was conducted by maceration using methanol and distilled water as solvents for 24 hours at room temperature, followed by filtration to collect the extracts. Methanol, a polar solvent, is known for its ability to extract both lipophilic and hydrophilic compounds, and it is easily removed at room temperature due to its volatility. Water, being a universal solvent, is preferred since most traditional preparations are water-based (Mahmoudi et al., 2013).

Highlighting Secondary Metabolites

We investigated the following secondary metabolites in the aqueous extract: polyphenols, flavonoids, anthocyanins, tannins, leucoanthocyanins, bound quinones, alkaloids, and saponins. Specific reagents were used for detection: Burton's reagent for polyphenols, SHINODA reagent for flavonoids, concentrated HCl for anthocyanins, $FeCl_3$ for tannins, Shinoda's reagent for leucoanthocyanins, Borntrager's reagent for bound quinones, and Dragerdorff's reagent for alkaloids. In the organic extracts, we tested for steroids and triterpenoids using Lieberman Burchard reagent, and free quinones using Borntrager's reagent.

Dosage of Polyphenolic Compounds

Determination of Total Polyphenols

The total polyphenol content was determined using the Folin-Ciocalteu method as described by Kapepula et al. (2016). The quantity of total polyphenols is expressed in mg of gallic acid equivalents (GAE) per gram of dry extract, based on the calibration equation:

$y = 1.7097 \ln(x) + 5.2062$

$R^2 = 0.965$, where x is the absorbance and y is the gallic acid equivalent (mg/g).

Total Flavonoid Assay

The total flavonoid content was estimated using a spectrophotometric method. Aluminum trichloride forms a yellow complex with flavonoids, absorbing at 415 nm (Mbadiko et al., 2019). The content is expressed as mg of quercetin equivalent (QE) per gram of dry extract:

$y = 0.5001 \ln(x) + 3.442$

$R^2 = 0.944$, where x is the absorbance and y is the quercetin equivalent (mg/g).

Total Anthocyanin Dosage

The anthocyanin content was determined according to Mbadiko et al. (2019), with results expressed in mg of catechin equivalent (CE) per gram of dry plant matter:

$y = 0.0728 x + 0.0171$

$R^2 = 0.994$, where x is the absorbance and y is the catechin equivalent (mg/g).

Evaluation of Antioxidant Activity

Sample Preparation

Ten mg of dry extract was dissolved in 1 mL of methanol for polar extracts and a dichloromethane-methanol mixture (1:1) for apolar extracts (solution A: 10 mg/mL). Dilutions were made to obtain concentrations of 8 mg/mL, 6 mg/mL, 4 mg/mL, and 2 mg/mL (Mayele et al., 2024).

ABTS and DPPH Tests

The antioxidant capacity was measured using ABTS and DPPH assays. ABTS forms a cationic radical when reacting with potassium or sodium persulfate. The decolorization of ABTS•+ after adding antioxidants was measured at 734 nm (Mayele et al., 2024). The DPPH• radical assay was

conducted as described by Kapepula et al. (2016), measuring absorbance at 517 nm.

Statistical Analysis

Data were analyzed by ANOVA followed by Tukey's test. Results were considered significant at p≤0.05p \leq 0.05p≤0.05. The IC50 values were calculated using GraphPad Prism 9.0, while the statistical analyses were performed using Statistix 8.0 software.

Determination of Anti-Inflammatory Activity

Anti-inflammatory activity was assessed using the protein denaturation method (Albumin) as described by Kumari et al. (2015). The reaction mixture consisted of egg albumin, PBS, and the extract at various concentrations. The percentage of protein denaturation inhibition was calculated as follows:

% Inhibition of denaturation = (1-D/C) × 100

Or :

D: Absorbance of the extract/positive control

C: Absorbance without extract (blank: negative control).

Antidiabetic Activity

For glucophage activity, the assay was conducted by mixing glucose solution with the extracts and incubating at 37°C. Glucose levels were measured using the glucose oxidase method.

RESULTS

Phytochemical Screening

The results of the phytochemical screening of *C. longa* rhizomes and *A. melegueta* and *P. guineensis* seeds are presented in **Table 1** below.

Table 1:

Qualitative phytochemical composition of rhizome extracts of ***C. longa***, seeds of ***A. melegueta*** and ***P. guineensis***, and bio-optimization (CAP)

	Aqueous extract				Organic extract			
	A. meleguata	*C. longa*	*P. guineensis*	CAP	*A. meleguata*	*C. longa*	*P. guineensis*	CAP
Polyphenol	+	+	++	+++	+	+	++	+++
Quinones	+	+	-	++	+	+	+	+
Anthocyanins	+	+	-	+	+	+	++	+
Flavonoids	+	+	++	+	+	+	++	+
Tannins	+	+	++	++	+	+	++	++
Terpenoids	-	+	-	++	-	-	-	++
Steroids	+	+	-	+	+	+	-	++
Alkaloids	+	+	+	+++	+	+	+	++++
Saponins	-	+	++	++	-	-	++	++

Legend: CAP = *C. longa* (50%) + *A. melegueta* (25%) + *P. guineensis* (25%).

During the analysis of the phytochemical composition of the extracts of the studied species, nine secondary metabolites were investigated: polyphenols, quinones, anthocyanins, tannins, terpenoids, steroids, alkaloids, and saponins. Among the polyphenols, flavonoids were specifically examined.

The extracts of *A. melegueta*, *C. longa*, *P. guineensis*, and their combination (CAP) contained, on average, 83.5% of the targeted secondary metabolites (78% for *A. meleguata*, 100% for *C. longa*, 56% for *P. guineensis*, and 100% for CAP) in the aqueous extracts. In contrast, the organic extracts contained, on average, 84% of the targeted metabolites (78% for *A. meleguata*, 78% for *C. longa*, 78% for *P. guineensis*, and 100% for CAP).

Notably, terpenoids and saponins were absent in the aqueous extract of *A. melegueta*, whereas quinones, anthocyanins, terpenoids, and saponins were absent in the aqueous extract of *P. guineensis*. Furthermore, in the organic extracts, terpenoids and saponins were absent in the extracts of *A. melegueta* and *C. longa*, while terpenoids and steroids were absent in the extract of *P. guineensis* **(Table 1)**.

Dosage Of Secondary Metabolites

Table 2 shows the contents of secondary metabolites in the rhizomes of *C. longa*, leaves of *A. melegueta*, and seeds of *P. guineensis*.

Table 2:

Phenolic compound content of aqueous and organic extracts of species (***A. melegueta***, ***C. longa***, ***P. guineensis***): Total polyphenols (mg EAQ/g dm), Flavonoids (mg EQ/g dm), Tannins (mg Ec/g dm), and Anthocyanins (%).

Excerpts	***Total polyphenols (mg EAQ/g ms)***	***Flavonoidsmg (EQ/g ms)***	***Tanninsmg Ec/g (EC/g of MS)***	***Anthocyanins (%)***
Aqueous extract				
A. melegueta	*399.085 ± 0.373*	*139.696 ±0.395*	*10.650 ± 0.082*	*30.66±0.003*
C. longa	*379.132 ± 0.351*	*260.976 ±0.114*	*33.985 ±0.063*	*40.003±0.04*
P. guineensis	*321.773 ± 0.799*	*226.391 ± 0.235*	*32.748 ±0.04*	*22.748 ±0.04*
CAP	*619,453±394*	*627,453±394*	*77.3 830±0.082*	*22,778±0.063*
Organic extract				
A. melegueta	*352.591 ± 0.175*	*243.366 ± 0.217*	*s16.357 ±0.253*	*18±0.003*
C. longa	*341.773 ± 0.799*	*236.391 ± 0.235*	*42.748 ±0.04*	*45.01±0.04*
P. guineensis	*321.773 ± 0.799*	*226.391 ± 0.235*	*40.746 ±0.04*	*42.748 ±0.04*
CAP	*1093,449±0.351*	*706,148*	*99,852±0.04*	*42.56 ±0.04*

Legend: CAP: *C. longa* (50%) + *A. melegueta* (25%) + *P. guineensis* (25%). EAQ/g of MS: Equivalent of gallic acid per gram of dry matter. EQ/g of MS: Equivalent of quercetin per gram of dry matter. EC/g of MS: Equivalent to catechin per gram of dry matter.

The assay of secondary metabolic compounds revealed that polyphenols were the most abundant secondary

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metabolites in both aqueous and organic extracts. The aqueous extracts of *A. melegueta* were richer in total polyphenols than those of *C. longa* and *P. guineensis*. In contrast, *C. longa* was richer in flavonoids. *C. longa* and *P. guineensis* contained higher tannin levels compared to *A. melegueta*, while *C. longa* had a higher anthocyanin content.

Antioxidant Activity

The results of the anti-radical activity of the plant extracts, expressed as inhibitory concentration 50 (IC50) values obtained from the DPPH and ABTS tests (mean ± SD, n=3), are presented in **Table 3**.

Table 3:
Anti-radical activity of plant extracts expressed as inhibitory concentration 50 (IC50) values by the DPPH and ABTS tests.

C. longa	172±1.80	119.8±2.75	20.56±1.56	10.08±0.00
A. melegueta	79.74±1.13	72.36±1.58	**266,467±107.11**	**95.62±0.027**
P. guineensis	97.5±2.885	61.07±1.43	**2070,567±314.95**	**129,230±48,313**
CAP	**127,230±48,313**	16.50±0.007	40,345±1,544	7.94±0.007
Galic acid	0.85±0.15	0.85±0.15	0.75±0.06	0.75±0.06

Our data demonstrated that all the species exhibited antioxidant activity against DPPH• and ABTS• radicals. However, stronger anti-radical activity was observed with the ABTS• radical than with the DPPH• radical **(Table 3)**. The aqueous extracts of *C. longa* and *A. melegueta* exhibited better antioxidant activity than their organic extracts against the DPPH• radical. In contrast, the organic extracts of *P. guineensis* and the CAP combination displayed superior antioxidant activity against the same radical. Regarding the ABTS• radical, the organic extracts of all species showed better antioxidant activity than their aqueous counterparts.

Remarkably, the CAP combination demonstrated higher anti-radical activity against DPPH• than the individual plants. However, against ABTS•, the antioxidant activities of the CAP aqueous and organic extracts were lower than those of *P. guineensis*, *C. longa*, and *A. melegueta*. Notably, only the organic extract of *C. longa* exhibited stronger activity than gallic acid against the ABTS• radical **(Table 3)**.

Anti-Inflammatory Activity

The results of the anti-inflammatory activity of *C. longa*, *A. melegueta*, *P. guineensis*, and the CAP combination are presented in **Table 4**.

Table 4:
Inhibition percentages of inflammatory action (%) of aqueous and organic extracts at different concentrations (13, 19, 25 mg/mL)

Concentration (mg/mL)	**13**	**19**	**25**
Aqueous extract			
C. longa	69.3 ± 0.07	89.5 ± 0.05	89.7 ± 0.04
A. melegueta	80.4 ± 0.05	85.4 ± 0.05	92.1 ± 0.05
P. guineensis	76.4 ± 0.04	80.4 ± 0.04	82.1 ± 0.04
CAP	96.7 ± 0.04	92.1 ± 0.05	90.0 ± 0.16
Diclofenac (control)	90.2	97.7	99.6
Organic extract			
C. longa	80.4 ± 0.05	82.1 ± 0.05	96.0 ± 0.16
A. melegueta	22.3 ± 0.83	29.7 ± 0.05	35.2 ± 0.05
P. guineensis	80.4 ± 0.04	85.4 ± 0.04	92.1 ± 0.04
CAP	95.02 ± 0.16	100 ± 0.05	112 ± 0.16
Diclofenac (control)	90.2	97.7	99.6

Legend: CAP: *C. longa* (50%) + *A. melegueta* (25%) + *P. guineensis* (25%).

Our results showed that all the tested species exhibited anti-inflammatory activity. We observed that the anti-inflammatory action increased with concentration for both aqueous and organic extracts, except for the aqueous extracts of the CAP combination. Although the anti-inflammatory action of the CAP aqueous extract decreased with increasing concentration, it remained higher than that of *C. longa* and *P. guineensis*. In contrast, the organic extract of CAP exhibited a stronger anti-inflammatory effect compared to the individual species.

Notably, the anti-inflammatory activity of the CAP combination was higher than that of the diclofenac sodium control **(Table 4)**.

Antidiabetic Activity

Figure 2A and **2B** show the antidiabetic activity of the organic and aqueous extracts of the different species.

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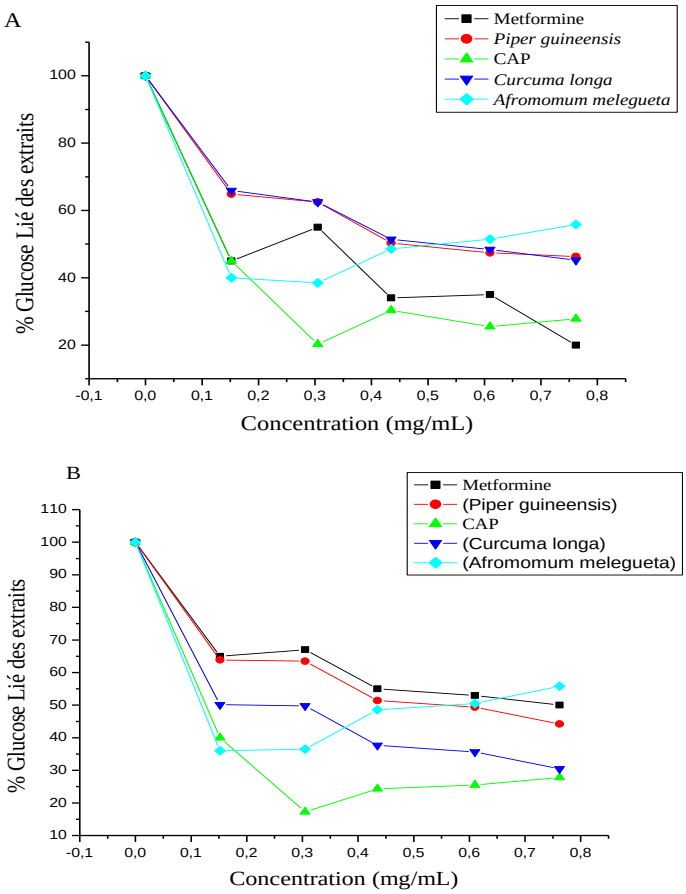
Figure 2:
Antidiabetic activity of ***C. longa***, ***A. melegueta***, ***P. guineensis***, and the CAP combination.

- **A:** Antidiabetic activity of aqueous extracts
- **B:** Antidiabetic activity of organic extracts



The data presented in these **Figures** demonstrate that all species and their combinations exhibit significant biological activity. We observed that the extract of *A. melegueta* showed stronger antidiabetic activity compared to the other two species at concentrations below 0.2 mg/mL. However, at concentrations above 0.2 mg/mL, the antidiabetic activity of *A. melegueta* appeared to decrease compared to the other species.

On the other hand, the CAP combination exhibited higher antidiabetic activity than the individual species, with its strongest effect observed at a concentration of 0.3 mg/mL. However, at concentrations above 0.3 mg/mL, the activity of CAP seemed to diminish **(Figure 2A).**

Furthermore, the organic extracts exhibited similar characteristics to the aqueous extracts. However, it was noted that the antidiabetic activity of *C. longa* was stronger than that of *P. guineensis* and *A. melegueta* at concentrations above 0.3 mg/mL. Remarkably, at concentrations above 0.8 mg/mL, the activity of *C. longa* appeared to be comparable to or even greater than that of the CAP combination **(Figure 2B)**.

The antidiabetic activity of CAP was superior to that of metformin at concentrations ≤ 0.65 mg/mL with the aqueous extracts and was significantly higher at a concentration of 0.8 mg/mL. It is important to note that the activities of all organic extracts were superior to that of the control. However, at concentrations above 0.65 mg/mL, the antidiabetic activity of *A. melegueta* was weaker compared to the control.

DISCUSSION

Phytochemical Screening

Numerous studies have shown that extracts from the rhizome of *C. longa* contain secondary metabolites such as polyphenols and tannins (Marchant et al., 2022; Mayele et al., 2024; Widowati et al., 2018), flavonoids, anthocyanins, alkaloids, and steroids (Mayele et al., 2024; Olatunde et al., 2014; Widowati et al., 2018), as well as quinones, alkaloids, terpenes, and resin (Olatunde et al., 2014). However, Olatunde et al. (2014) reported that flavonoids, tannins, saponins, and phenols were absent in ethanolic extracts of *C. longa* rhizome. Similarly, Mayele et al. (2024) indicated that saponins were absent in their sample of *C. longa* rhizome.

In contrast, the ethanolic extracts of *A. melegueta* seeds contain tannins, saponins, flavonoids, steroids, and alkaloids. Most of these metabolites are also found in the methanolic extracts of its seeds, except for saponins and terpenoids; however, the presence of resin has been noted (Toh et al., 2019). Additionally, the methanolic extracts of *P. guineensis* leaves and seeds exhibit a rich phytochemical profile, containing alkaloids, glycosides, tannins, flavonoids, terpenes, sesquiterpenoids, monoterpenoids, and saponins.

The differences in phytochemical compositions between our results and those reported in previous studies may be attributed to variations in geography, light sources, or the solvents used during extraction. Furthermore, many bioactive molecules, such as curcumins (polyphenol:

curcuminoids) in the rhizome extract of *C. longa* (Quiros-Fallas et al., 2022), hydroxyphenylalkylene and diarylheptanoids in *A. melegueta* seed extract (Abdou et al., 2021), and piperine (alkaloid) in the genus *Piper* (Liu et al., 2020), have been identified.

Dosage of Secondary Metabolites

A. melegueta, *C. longa*, and *P. guineensis* are species known to be rich in secondary metabolites (Alagbe et al., 2021; Mohammed et al., 2017; Toh et al., 2019). Phenolic compounds are the most abundant in these three species (Alagbe et al., 2021; Quiros-Fallas et al., 2022). For instance, among the polyphenols in the crude extract of *C. longa*, curcumin constitutes approximately 70–76%, dimethoxycurcumin 16%, and bisdemethoxycurcumin 8% (Olatunde et al., 2014).

The total polyphenols, flavonoids, and tannins content of the aqueous and organic extracts from the CAP combination were on average 1.74, 3.22, and 3.99 times higher, respectively, than those of the aqueous extracts alone.

Antioxidant Activity

Several studies have documented the significant antiradical activity of *A. melegueta* seeds, *C. longa* rhizomes, and *P. guineensis* (Alagbe et al., 2021; Marchant et al., 2022; Mayele et al., 2024; Omoba et al., 2019; Quiros-Fallas et al., 2022). The high antiradical activity observed in the CAP combination is attributed to the synergistic effects of these plants when used together. This activity is largely attributed to their rich phytochemical compositions.

Radicals often react simultaneously with polyphenolic and non-polyphenolic compounds, such as the ABTS• radical (Mutwale, 2017, as cited in Mayele et al., 2024), indicating a possible synergy between these compound groups (Mayele et al., 2024). Curcuminoids isolated from *C. longa* rhizomes (Quiros-Fallas et al., 2022; Zhang et al., 2013) and piperine from *Piper* spp. (Liu et al., 2020) contribute significantly to this antiradical activity. Additionally, the presence of polyphenols in *A. melegueta*, particularly flavonoids (Toh et al., 2019), enhances the antioxidant capacity of the CAP combination. The combination of curcumin and piperine has been shown to improve oxidative stress management, with curcumin exhibiting enhanced activity when combined with piperine (Sehgal et al., 2011).

Anti-inflammatory Activity

Studies have shown that *A. melegueta* and *P. guineensis* exhibit anti-inflammatory activity (Abdou et al., 2021; Alagbe et al., 2021; Omoba et al., 2019). Additionally, *C. longa* has demonstrated the ability to reduce free radicals (Marchant et al., 2022; Quiros-Fallas et al., 2022). The anti-inflammatory properties of these plants are primarily linked to their phytochemical constituents (Abdou et al., 2021; Omoba et al., 2020; Toh et al., 2019; Alagbe et al., 2021).

Curcumin, for example, exerts its anti-inflammatory effect by inhibiting LOX and COX enzymes, which are generally elevated during inflammatory conditions such as cancer (Nyamangombe et al., 2024). It also modulates the production of inflammatory cytokines and prostaglandins, including TNF-α, IL-1β, MIP-1β, MCP-1, and IL-8 (Cianciulli et al., 2016).

Aframomum melegueta has also been reported to stabilize the cell membrane of injured tissues, promoting regeneration and exhibiting potent antioxidant properties. It has been used successfully to treat inflammation-related diseases, including cardiovascular disease, arthritis, osteoporosis, and Alzheimer's disease. Piperine, a bioactive component from *Piper* spp., significantly inhibits the production of pro-inflammatory mediators IL-6 and PGE (Abdou et al., 2021).

Costantini et al. (2022) reported that curcumin functions as an anti-inflammatory agent comparable to steroidal and non-steroidal drugs, such as indomethacin and phenylbutazone. Curcumin inhibits pro-inflammatory transcription factors, including nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1), as well as nuclear factor erythroid 2-related factor 2 (Nrf2) and signal transducers and activators of transcription (STAT-1, -3, -4) (Sharifi-Rad et al., 2020). It decreases macrophage activity, thereby reducing the production of inflammatory cytokines (Kanoune, 2021).

Omosa et al. (2017) demonstrated that crude extracts of *C. longa* exert anti-inflammatory effects in collagen-induced arthritis models in male rats. Additionally, a curcumin

derivative, bisdemethylcurcumin, has been identified as a potent anti-inflammatory agent due to its suppression of TNF-α-induced NF-κB activation. Furthermore, Liju et al. (2011) demonstrated that turmeric oil exhibits significant anti-inflammatory activity in both acute and chronic inflammation models, notably in carrageenan- and dextran-induced rat paw edema.

Antidiabetic Activity

According to the results of Mayele et al. (2024) and Widowati et al. (2018), *C. longa* rhizome extract exhibits antidiabetic properties. Olatunde et al. (2014) demonstrated that the aqueous extract, when administered orally, significantly reduced blood glucose levels compared to the control group. This activity is attributed to curcuminoids, including bisdemethoxycurcumin and curcumin, which inhibit the activity of α-glucosidase (Widowati et al., 2018).

The leaves and seeds of *A. melegueta* exhibit antihyperglycemic activity and improve β-cell dysfunction and other complications related to diabetes (Mohammed et al., 2017). In addition, Nguele et al. (2017) showed that extracts from certain species of the genus *Aframomum* spp. reduced the exponential weight gain promoted by an atherogenic diet. They also observed a reduction in total and LDL cholesterol levels, along with an increase in HDL cholesterol levels, thereby reducing the risk of obesity, which is recognized as a primary factor for type 2 diabetes (Karlsson et al., 2013).

Besides *C. longa* and *Aframomum* spp., species of the genus *Piper* spp. also possess antidiabetic properties. Liu et al. (2020) demonstrated that piperine, when administered to obese mice, significantly decreased fasting blood glucose levels, serum total cholesterol, and total triglyceride levels while improving glucose intolerance and insulin resistance. The strong activity observed in this study may be attributed to a possible combined effect or synergy between the phytochemicals present in each species.

The effectiveness of curcumin in vivo is often limited by its low absorption rate and rapid metabolism. However, its combination with piperine enhances its bioavailability by inhibiting the enzyme responsible for its metabolism (Cho et al., 2024). The biological activity of curcumin combined with piperine is significantly stronger than that of curcumin alone (Partial et al., 2015). Piperine not only improves digestion by stimulating pancreatic enzymes but also decreases food transit time from the gastrointestinal tract, increases saliva production, and enhances gastric secretions (Cho et al., 2024).

The bioavailability of curcumin can be enhanced by increasing its absorption and decreasing its metabolic clearance. Stati et al. (2021) reported that co-administration of curcumin with natural UDP-glucuronyl transferase (UGT) inhibitors, such as piperine, improves the bioavailability of curcumin compared to its administration alone. Curcumin administered at 2 g/kg achieves a low serum concentration over 4 hours, whereas co-administration with 20 mg/kg piperine significantly increases its serum concentration for a short period of 1 to 2 hours post-administration. Additionally, co-administration of piperine with curcumin significantly reduces the elimination and half-life of curcumin (Nebrisi, 2021).

Piperine influences several enzymatic biotransformation reactions in liver tissue, both in vitro and in vivo. It acts as a non-specific inhibitor of drug metabolism without discriminating between different forms of cytochrome P450 (Stati et al., 2021). The overall increase in curcumin bioavailability with piperine is approximately 2000% (Shoba et al., 1998). The separate consumption of turmeric and piperine is generally safe and has been associated with a protective effect against cardiovascular mortality (Sheikhi et al., 2019; Cousin et al., 2022).

Ahmad et al. (2014) reported that *C. longa* has antidiabetic, hepatoprotective, and antioxidant properties. Administration of the methanolic extract to alloxan-induced diabetic rabbits significantly improved serum glucose levels, serum transaminase levels, and antioxidant activity, while the aqueous extract stimulated insulin secretion from pancreatic tissue in both hypoglycemic and hyperglycemic conditions. This extract also enhanced glucose uptake from abdominal muscle tissue in the presence and absence of insulin (Mohankumar & McFarlane, 2011).

Khan et al. (2014) found that turmeric ethyl acetate extract exhibits a higher protein glycation inhibitory potential compared to ascorbic acid. The methanolic extract also

displayed anti-glycation activity with a minimum inhibitory concentration (MIC50) of 324 µg/ml. Moreover, the antidiabetic capacity of *C. longa* volatile oil, in terms of its ability to inhibit glucosidase activities, was found to be more effective than the standard reference drug acarbose. Ar-turmerone, the major volatile component in the rhizome, exhibited potent inhibition of α-glucosidase (IC50 of 0.28 µg) and α-amylase (IC50 of 24.5 µg) (Lekshmi et al., 2012).

Additionally, curcuminoids and sesquiterpenoids from *C. longa* have been shown to suppress an increase in blood glucose levels in type 2 diabetic mice (Omosa et al., 2017). This is significant given that elevated blood glucose is a critical factor in microvascular complications (Vafaeipour et al., 2022). Curcumin and other bioactive compounds present in turmeric are proposed as hypoglycemic agents, promoting insulin regulation, enhancing insulin sensitivity, and decreasing cellular glucose uptake (Zhang & Kitts, 2021).

Vafaeipour et al. (2022) demonstrated that turmeric's effects on diabetes include lowering blood glucose and glycosylated hemoglobin (HbA1c). Curcumin, based on its antioxidant properties, may also regulate insulin resistance (Karłowicz-Bodalska et al., 2017). It lowers blood glucose levels by reducing hepatic glucose production and stimulating glucose uptake through upregulation of genes such as glucose transporter 4 (GLUT4), GLUT2, and GLUT3 (Ghorbani et al., 2014).

Zhang et al. (2021) reported that the ethanol extract of *C. longa* could serve as a functional food ingredient for the prevention or management of type 2 diabetes (T2D), primarily due to compounds like 1,3-demethoxycurcumin and bis-demethoxycurcumin, which activate peroxisome proliferator-activated receptor γ (PPARγ). Curcumin can induce PPAR-γ activation, reduce plasma glucose levels, activate glycolysis enzymes, stimulate hepatic glucokinase, increase hepatic glycogen content, and downregulate gluconeogenesis enzymes by inhibiting glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activity (Vafaeipour et al., 2022).

Antidiabetic Activity

Type 2 diabetes (T2D) is closely associated with obesity (Shao-Ling et al., 2009). Impaired insulin sensitivity related to obesity is thought to result from high concentrations of free fatty acids in plasma and tissues, leading to lipotoxicity responsible for muscle insulin resistance (Alappat & Awad, 2010; Lecerf, 2012). Additionally, elevated levels of pro-inflammatory cytokines have been observed in insulin resistance associated with obesity and T2D (Shao-Ling et al., 2009).

In obesity, insulin resistance is primarily induced by free fatty acids, which mediate NF-κB activation. NF-κB plays a critical role in the development of insulin resistance (Alappat & Awad, 2010). Its activation leads to the overproduction of TNF-α and IL-6 in adipocytes, which can disrupt the transcriptional activity of insulin receptor substrate-1 (IRS-1) and transporter proteins such as GLUT4 (Alappat & Awad, 2010). Consequently, the role of curcumin as an NF-κB inhibitor is significant in reducing insulin resistance (Shao-Ling et al., 2009).

Obesity is also associated with increased levels of endoplasmic reticulum (ER) oxidative stress in adipose tissues and the liver. Curcumin reduces ER stress and increases the gene expression of Sirtuin 1 (Sirt1) and other transcription factors, which improves insulin sensitivity. Moreover, the accumulation of advanced glycation end products (AGEs) in the body, resulting from the non-enzymatic glycation of proteins, is linked to various pathological conditions, including aging and diabetes mellitus. Turmeric ethyl acetate extract exhibits a protein glycation inhibitory potential 800 times higher than that of ascorbic acid, while the methanolic extract shows anti-glycation activity with a minimum inhibitory concentration (MIC50) of 324 µg/ml (Khan et al., 2014).

In obese mice with leptin deficiency, curcumin has been shown to decrease glycated hemoglobin (HbA1c) levels and improve insulin sensitivity by activating glycolysis and inhibiting hepatic gluconeogenesis. In diabetic rats induced by a high-fat diet and streptozotocin, curcumin, administered at doses of 50, 150, and 250 mg/kg body weight, significantly reduced blood glucose levels and improved insulin resistance in skeletal muscle. This effect was achieved by increasing glucose and fatty acid oxidation, enhancing the expression of AMP-activated protein kinase (AMPK), promoting fatty acid uptake, and increasing the expression of carnitine palmitoyltransferase

I (CPT-1), which is involved in mitochondrial fatty acid oxidation. Additionally, curcumin inhibited the expression of pyruvate dehydrogenase (glycolysis) and glycogen synthase (Lecerf, 2012).

The use of synthetic curcumin analogs, such as ferulamides, has been proposed for managing hyperglycemia associated with metabolic syndromes (Alappat & Awad, 2010). Curcumin's hypoglycemic and antidiabetic effects in pancreatic β-cells are linked to its ability to mitigate high glucose-induced insulin resistance. In cultured rat insulinoma cells (INS-1), a model for studying insulin secretion from pancreatic β-cells, curcumin increased insulin expression and secretion through the activation of phosphatidylinositol-3-kinase (PI3K), protein kinase B (Akt), and the glucose transporter 2 (GLUT2) signaling pathway.

Furthermore, curcumin enhances the phosphorylation of the insulin receptor (IR), IRS-1, PI3K, and Akt, leading to increased expression of pancreatic and duodenal homeobox-1 (PDX-1) and decreased insulin mRNA levels. This process is associated with elevated levels of GLUT2 and glucokinase (GCK) activity, which are essential for regulating cellular glucose uptake and metabolism (Zhang et al., 2021).

CONCLUSION AND SUGGESTIONS

Our work focused on the study of the biological activities of *Curcuma longa* L., *Aframomum melegueta*, *Piper guineensis*, as well as the bio-optimization of turmeric in a mixture called "CAP BIO." At the end of this study, we demonstrated that these different plants are exploitable, as both the individual plants and their combination in the mixture CAP BIO represent an important source of secondary metabolites that contribute to the proper functioning of the body and help prevent the occurrence of chronic non-communicable diseases such as diabetes.

This study confirmed the antioxidant, antidiabetic, and anti-inflammatory activities of the individual plants and the mixture. The fact that the different plants simultaneously exhibit several biological activities makes this mixture a promising candidate for the management of diabetes. Our results suggest that in vivo antioxidants (polyphenols or others) from plants, in this case *C. longa*, could inhibit or delay the clinical manifestations of diabetes by scavenging excessively produced free radicals, inhibiting enzymes or other biomolecules involved in free radical production, or stimulating the synthesis of enzymes of the antioxidant defence system.

It should be noted that these activities were assessed in vitro, and the plants were not harvested from the same geographical region, which may explain differences in metabolite content. Therefore, in vivo studies of antioxidant, antidiabetic, and anti-inflammatory activities are desirable for the individual plants as well as for the mixture CAP BIO to confirm any synergistic effects on improving the biological activities of the mixture.

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