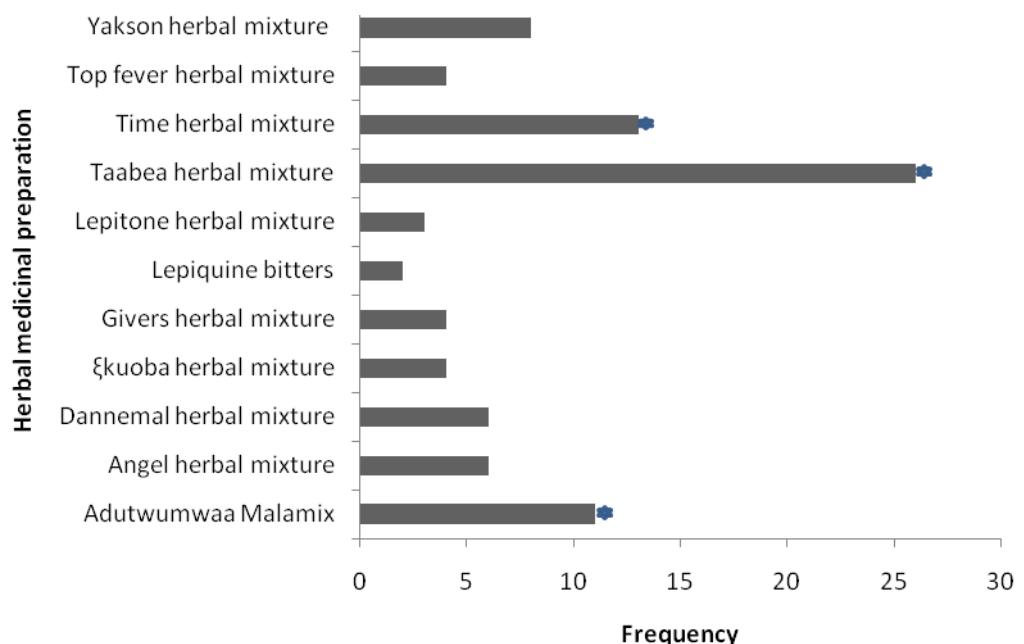
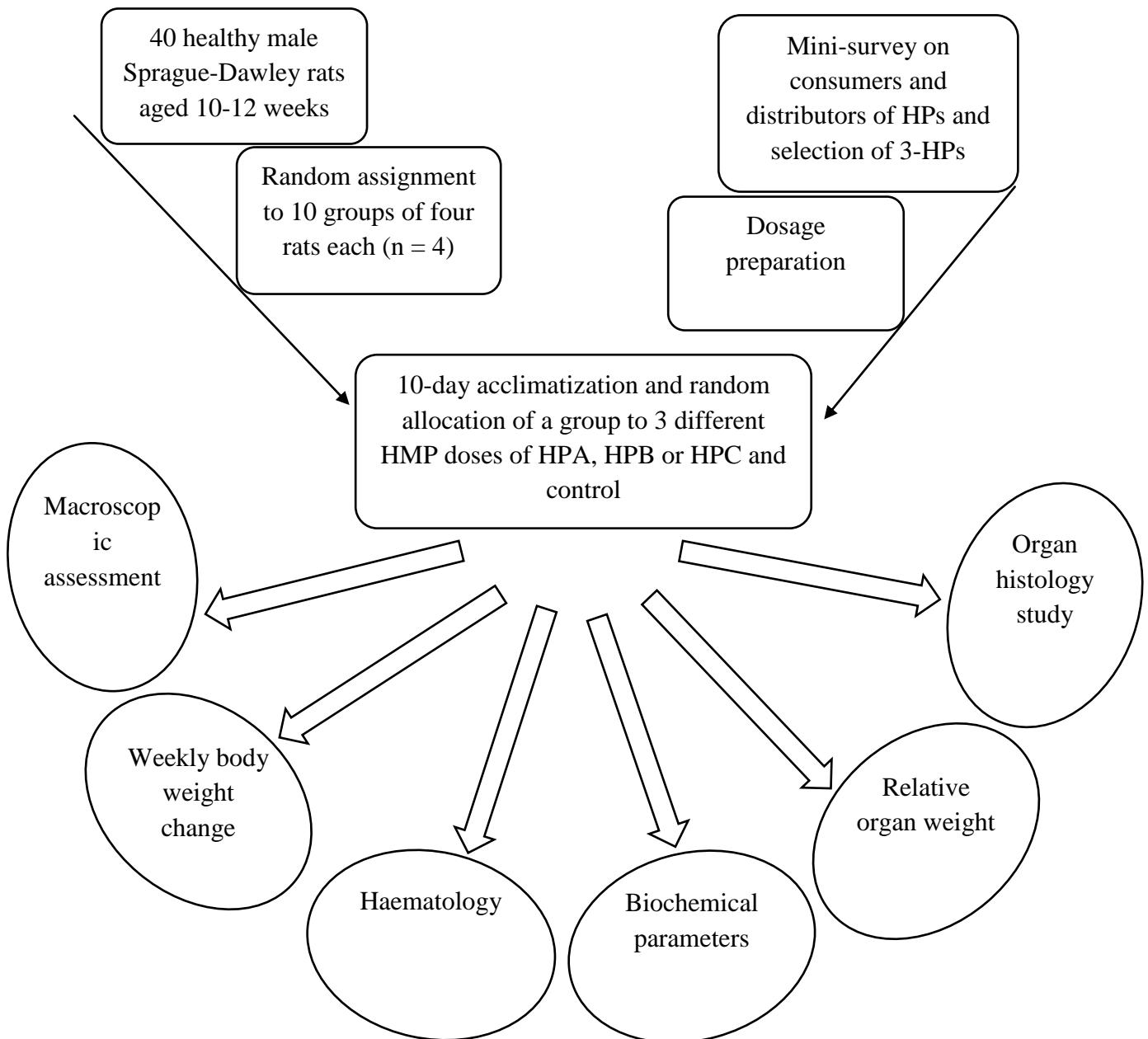


## **SUPPLEMENTARY FIGURES**



**Supplementary Figure 1:** Top-three commonly patronized antimalarial herbal medicinal preparations among surveyed participants in the Kumasi metropolis of Ghana<sup>20 22</sup>. The bars with the star represent the top-three most patronized herbal medicinal products selected for further *in vivo* sub-chronic toxicity study.



**SupplementaryFigure 2:** Study design. The macroscopic, haematological, biochemical, relative organ weights and organ histology studies performed on both test group rats and the control rats.

## **SUPPLEMENTARY TABLES**

**Supplementary Table 1:** Ethno-medicinal uses of the medicinal plant constituents

<b>Medicinal plants</b>	<b>Ethnomedicinal uses with reference sources</b>	<b>Documented safety data</b>	<b>Herbal product</b>
<i>Cola gigantea</i>	Stem barks are used for inflammation and bacterial infections. <sup>1</sup> The plant is used in folklore medicine as a heart anti-depressant.	<i>C. gigantea</i> oil extract is believed to possess general cellular toxicity effect due to reactive oxygen species production and oxidative stress. <sup>2</sup>	Time herbal mixture
<i>Solanum torvum</i>	Leaves and the unripe fruits are used to treat tuberculosis, <sup>3</sup> <i>S. torvum</i> plant is used to treat diabetes, <sup>4</sup> epilepsy, <sup>5</sup> parasitic infections and to reduce oxidative stress on the liver. <sup>6</sup> Extracts from the aerial parts of the plant also have anticancer properties. <sup>7</sup> The plant is also used in Ghana to treat malaria. <sup>8,9</sup>	Acute administration of <i>S. torvum</i> was observed to be safe in broiler chickens. <sup>10</sup> <i>S. torvum</i> has the potential in preventing the nephrotoxicity induced by doxorubicin. <sup>11</sup> Aqueous fruit extracts had hypotensive effects and were chronically save in rats. <sup>12</sup>	
<i>Spathodea campanulata</i>	Used for the treatment of malaria, <sup>13</sup> cancer and for healing of wounds. <sup>14</sup>	Acute administration of ethanolic leaf extract was observed to be save in rats, <sup>15</sup> however chronic administration resulted in loss of weight, sluggish movement and significant but reversible hepatotoxic effect. <sup>16</sup>	
<i>Bombaxbuono pozzense</i>	Used to treat sleeping sickness. Ethanol extract of the stem bark is also believed to have antitrypanosomal activities. <sup>17</sup>	Activated spines of <i>B. buonopozense</i> is reported to have high biosorption for copper and zinc metals, and may lead to bioconcentration of these metals in <i>B. buonopozense</i> plant products. <sup>18</sup>	
<i>Vernonia amygdalina</i>	Leaf extract of <i>V. amygdalina</i> have been reported to affect multiple stages of Plasmodium life cycle, <sup>19,20</sup> leukemia <sup>21</sup> and prostate cancer. <sup>22</sup> It is also used for hepatoprotection. <sup>23,24</sup>	Reported to have chromosomal aberrations effect. <sup>25</sup> Aqueous leaf extract of the plant were observed to have nutritional, clinical and veterinary relevance with no serious hepatotoxic effects in rats. <sup>26</sup>	
<i>Ocimum viride</i>	Ethanol extract of the essential oils from the aerial parts of <i>O. viride</i> has anticancer activity against human colorectal adenocarcinoma cells (COLO 205 cell line). <sup>27</sup> <i>O. viride</i> extract also possess high antimicrobial properties against <i>Rhizopus stolonifer</i> , <i>Aspergillus</i> sp, and <i>Fusarium</i> sp. <sup>28</sup>	Ethanol extract of aerial parts of <i>O. viride</i> showed apoptosis properties inducing cytotoxic effect in human colorectal adenocarcinoma cells (COLO 205 cell line) death. <sup>28</sup>	Taabea herbal mixture
<i>Azadirachta indica</i>	Different parts of the plant are used to treat malaria <sup>29,30</sup> , cancer, ulcer, diabetes <sup>31</sup> , dengue fever, <sup>32</sup> chicken pox and dermal complications. <sup>31</sup>	Acute and 28-day subacute toxicity tests with <i>A. indica</i> fruit oil showed no significant difference in biochemical and haematological parameters, however, at high doses, signs of testicle, liver and kidneys toxicities were observed in histology slides. <sup>33</sup> Seed oil extract was observed by Gandhi and colleagues <sup>33,34</sup> to cause dose-dependent toxicity on the lungs and central nervous system in both rats and rabbits. <sup>34</sup> An 8-week study with aqueous leaf suspensions showed multi organ toxicities, tremours and loss of weight in goats and guinea pigs. <sup>35</sup>	
<i>Tetrapleurum raptera</i>	Used in West Africa for the treatment of malaria, <sup>36,37</sup> diabetes and hypertension, inflammation, <sup>38</sup> ulcer, and for the management of epilepsy and childhood convulsions. <sup>39</sup> Extracts of the plant also has a well-studied anti-molluscicide activities for the control of unwanted mollusc vectors. <sup>40</sup>	Edet and Ikpi <sup>41</sup> showed that aqueous fruit extract caused dose dependent mortality in the catfish fingerlings. At high doses, they also observed erratic swimming and loss of balance in the fingerlings. <sup>42</sup>	
<i>Cymbopogon citratus</i>	Leaf infusion has been used in folklore medicine to treat fever and malaria, <sup>43,44</sup> inflammatory conditions, <sup>44</sup> antifungal infestations <sup>45</sup> and epilepsy. <sup>46</sup>	Oils of <i>Cymbopogon citratus</i> showed a dose-dependent significant functional toxicities to stomach and liver of the Wistar rat during 14-day toxicity study at doses higher than 1500 mg/kg body weight, the oil was safe at doses less than 1500 mg/kg body weight. <sup>47</sup>	
<i>Moringa oleifera</i>	The plant is used for treating malaria, <sup>48</sup> diabetes, cancer, <sup>49</sup> and for the treatment of inflammatory-mediated chronic disorders. <sup>50</sup>	<i>Moringa oleifera</i> was observed by Asare and colleagues, <sup>51</sup> to exhibit genotoxic at supra-supplementation levels of 3000 mg/kg body weight in rats, but in the same study, they observed intake levels ≤ 1000 mg/kg body	

		weight to be safe in humans. <sup>51</sup> It has also been reported to be safe with no reported toxicity cases in humans. <sup>52</sup>	
<i>Anthocleistan obilis</i>	The plant is used to treat diverse health conditions. It is employed as antidiabetic, antimalarial, antimicrobial, hypotensive, spasmogenic, anti-obesity, antiulcerogenic, analgesic, anti-inflammatory, antioxidant, antitrypanosomal, anthelmintic and fertility agent. <sup>53</sup>	Acute toxicity study of root bark ethanol extract in mice showed toxic neurologic effect and the LD <sub>50</sub> at 24 h was 200 mg/kg. In the same study, the oral administration of 67 mg/kg ethanol extract attenuated hepatotoxicity in mice induced by CCl <sub>4</sub> . <sup>54</sup> Not much data is available concerning safety toxicity of the plant in humans. <sup>55</sup>	Adutwumwa amalamix
<i>Vitexgrandifolia</i>	The bark of the tree is employed for stomachic purposes and to treat diarrhoea, bronchial complaints, rickets, sores and fever. <sup>56</sup> Also used against malaria, yellow fever, filarial and dengue vector control due to its larvicidal activity. <sup>57</sup> In traditional medicine, the leaves of <i>V. grandifolia</i> are used to treat diabetes mellitus and as a diuretic in the treatment of high blood pressure. <sup>58</sup>	Prolonged exposure of <i>V. grandifolia</i> is reported to have toxic effects in Sprague-Dawley albino rats, <sup>58</sup> . Observed signs include significant alterations in the architecture of the liver, kidney and lungs in the treated groups compared with the control, significant increase in the serum electrolytes, creatinine, and liver function enzymes in the dosed dependent manner. In addition, signs including polydipsia, polyuria, puffiness of hair, and calmness were reported in rats. <sup>59</sup>	
<i>Phyllanthusfraternus</i>	Used in Ayurveda and Siddha medicine for the treatment of jaundice and possible anti-DNA polymerase activity of the hepatitis virus. <sup>60</sup> The aerial parts of this plant is also believed to have anti-hepatotoxic activity. <sup>62,62</sup>	Hepatoprotective and antioxidant property of the aqueous extract of <i>P. fraternus</i> observed by Lata and colleagues on mice previously administered with cyclophosphamide. They observed normalizing of pathological and antioxidant parameters of the cyclophosphamide poisoned mice after <i>P. fraternus</i> administration. <sup>63</sup>	

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**SupplementaryTable 2:** Dosage forms used in this study compared to daily adult human doses (DAHD)

Herbal product	Given code	Dosage in test animals (mg/kg body weight)	Dosage in test animals compared to DAHD (daily dosage for 70 kg man)
Control group	Control.	Normal saline	0
Herbal product 1	HPA(1)	469.98	1x
	HPA(5)	2349.91	5x
	HPA(10)	4699.80	10 x
Herbal product 2	HPB(1)	399.96	1 x
	HPB(5)	1999.80	5 x
	HPB(10)	3999.60	10 x
Herbal product 3	HPC(1)	774.00	1 x
	HPC(5)	3870.00	5 x
	HPC(10)	7740.00	10 x

HPA(1) is the least dose of herbal preparation ‘A’ and equivalent to DAHD indicated, 5 times HPA(5) and 10 times HPA(10) is the middle and highest doses for herbal preparation ‘A’ respectively. It was repeated for herbal products ‘B’ and ‘C’ with respect to their corresponding DAHD as indicated

**SupplementaryTable 3:** Basic information of the herbal product.

Drug number	Name of Product	Conc. (mg/5ml±sem)	Normal DAHD (ml/70kg/day)	Normal DAHD (mg/kg/day)	Indications
1	Taabea Herbal Mixture	26.11±1.55	90	469.98	malaria, loss of appetite
2	Time Herbal Mixture	22.22±2.66	90	399.96	malaria, loss of appetite, general body pains
3	AdutwumwaaMalamix	43.00±1.16	90	774.00	Malaria

Determined concentrations in 5mL of each preparation; their daily adult human dose (DAHD) (ml/70kg/day), their determined concentrations for the daily human doses (mg/kg/day), their major constituents and their indications on the label.

**SupplementaryTable 4:** Summary of weekly weight change and haematology results

Parameter	HPA(1), HPA(5) and HPA(10)	HPB(1), HPB(5) and HPB(10)	HPC(1), HPC(5) and HPC(10)
BWC W1	NSD	NSD	NSD
BWC W2	NSD	NSD	NSD
BWC W3	NSD	NSD	NSD
BWC W4	NSD	NSD	NSD
HCT (%)	NSD	NSD	NSD
MCV (fL)	NSD	NSD	NSD
MCH (pg)	NSD	NSD	NSD
MCHC (g/dL)	NSD	NSD	NSD
Platelet ( $\times 10^3/\mu\text{L}$ )	NSD	NSD	NSD
Lymphocytes (%)	NSD	NSD	NSD
MXD (%)	NSD	NSD	NSD
Neutrophils (%)	NSD	NSD	NSD
LYM #( $\times 10^3$ )	NSD	NSD	NSD
MXD #( $\times 10^3$ )	NSD	NSD	NSD
NEUT #( $\times 10^3$ )	NSD	NSD	NSD
RDW_SD (fL)	NSD	NSD	NSD
RDW_CV (fL)	NSD	NSD	NSD
PDW (fL)	NSD	NSD	NSD

‘NSD’ represents no significant difference between the control group and the dosed group at 95% CI. Key: BWC W represents body weight change for weeks (1, 2, 3 and 4). Red blood cell count (RBC), white blood cell count (WBC), granulocyte count (GRA), lymphocyte count (LYM), haemoglobin (HGB), hematocrit (HCT), mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelet count (PLT), platelet distribution width (PDW), mean platelet volume (MPV) and platelet larger cell ratio (P-LCR), Mixed cell count (MXD) consisting of *monocytes, eosinophils, basophil*.