

MINI-REVIEW

Transformative natural product-drug combinations: Advancing techniques to enhance efficacy against drug-resistant pathogens

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Abstract

This review explores the development, modification, and optimization of potent active compounds using combinatorial synthetic methods that incorporate phytoconstituents from plant extracts, aiming to enhance efficacy and mitigate resistance. Attenuated total reflectance-Fourier transform infrared spectroscopy, gas chromatography-mass spectrometry (GC-MS), and antibacterial data from the literature were employed to validate these strategies. The methodology emphasized precise harvesting, pre-treatment, and extraction processes to ensure the quality and efficacy of the plant extracts. Various extraction methods and solvents were used to isolate specific phytoconstituents, followed by further purification through chromatography. The review proposes three strategies: (i) reacting single or multiple plant extracts with reagents such as acids or catalysts, (ii) combining plant extracts with ineffective drugs to induce structural changes that enhance antibacterial efficacy, and (iii) integrating plant extracts with drugs not originally intended for the target disease to explore new structural functionalities. Significant findings include synergistic effects observed when *Psidium guajava* and *Calotropis procera* extracts were combined with antibiotics, leading to substantially increased zones of inhibition against resistant bacteria. GC-MS analysis identified numerous bioactive compounds, some of which with known anticancer properties, suggesting potential applications beyond antibacterial effects. These innovative combinatorial approaches demonstrate the potential to yield new compounds with enhanced pharmacological properties, highlighting the critical role of plant extracts in drug discovery and development. This review underscores the promise of harnessing natural products to combat multi-drug resistance, paving the way for advanced research and development in pharmaceutical applications.

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1. Introduction

Drug resistance represents a pressing global challenge that impacts clinical, community, and environmental health, as well as food security and development. The emergence

of antimicrobial resistance (AMR) complicates treatment efficacy by enabling pathogens to evolve mechanisms that resist drug therapy, leading to persistent infections and increased transmission rates. According to Cesur and Demiröz¹ and Olga *et al.*,² this phenomenon not only endangers health outcomes but also amplifies the burden on healthcare systems worldwide. The World Health Organization³ underscores the severity of the issue, reporting that AMR causes approximately 700,000 deaths annually. Projections indicate that this figure could escalate to 10 million deaths per year by 2050 if effective interventions are not implemented. Several interrelated factors, such as overuse and misuse of antibiotics in medicine, agriculture, and animal husbandry, drive the escalation of AMR. Practices such as over-prescription, self-medication, and the use of antibiotics as growth promoters in livestock exacerbate the problem.⁴ The pipeline for new antibiotics is worryingly sparse due to significant financial and scientific barriers faced by pharmaceutical companies.⁵ Moreover, environmental pollution and climate change contribute to the spread and mutation of resistant pathogens, further complicating efforts to control AMR.^{4,6}

1.1. Addressing AMR with medicinal plant compounds

The production of bioactive compounds from medicinal plants necessitates the use of sophisticated techniques to ensure scalability and efficiency. Direct extraction can be impractical, prompting the need for semi-synthesis, total synthesis, and biotechnological approaches as viable alternatives. Semi-synthesis involves modifying natural compounds to enhance their efficacy or ease of production. A notable example is the production of the critical anticancer drug paclitaxel (Taxol). Advances in synthetic chemistry have enabled the development of total synthesis routes for compounds like paclitaxel and its derivatives, improving availability and reducing the costs associated with natural extraction methods.^{7,8} Biotechnological methods, including genetic engineering and microbial fermentation, have revolutionized the production of complex natural products. For instance, genes responsible for paclitaxel biosynthesis have been successfully integrated into microorganisms such as *Escherichia coli* and *Saccharomyces cerevisiae*, enabling these microbes to produce paclitaxel precursors.⁷ In addition, plant cell culture techniques have been employed to cultivate paclitaxel from *Taxus* cell cultures.^{8,9} The semi-synthesis of bioactive terpenoids, steroids, and polyketides from uncultivated bacterial symbionts demonstrates the potential of these approaches.^{10,11} Biotechnological advancements, including plant tissue culture and microbial fermentation, highlight

the feasibility of producing these compounds at scale.¹² Genetic engineering has also been utilized to produce complex natural products like artemisinin through yeast, addressing challenges associated with traditional extraction methods from *Artemisia annua*.¹¹

1.2. The role of medicinal plants in combating AMR

Medicinal plants are rich sources of diverse phytochemicals, the composition of which varies depending on the plant species, its geographical location, and the extraction solvent used.¹³⁻¹⁶ Studies by Khosravi,¹⁷ Alzohairy,¹⁸ and Jafarnejad *et al.*¹⁹ suggest that aqueous plant extracts may effectively treat bacterial infections, sometimes showing comparable or even superior efficacy to certain antibiotics while potentially reducing the development of bacterial resistance. Drug repurposing also offers a promising strategy in the fight against drug-resistant pathogens. This approach involves using known compounds or existing drugs to treat recalcitrant infections and diseases.²⁰ Moreover, two potent bioactive compounds with diverse pharmacological activities present new opportunities for treating resistant infections. For example, the triple synergistic inhibitory activities of riboprine and forodesine against the enzymes RNA-dependent RNA polymerase, exonuclease, and adenosine kinase in the replication of severe acute respiratory syndrome coronavirus 2.^{21,22}

This review explores strategies to develop, modify, or optimize potent active compounds using a combinatorial synthetic method that utilizes phytoconstituents present in plant extracts. The aim is to enhance their efficacy and reduce the potential for pathogen resistance to existing or new compounds. Evidence from attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR), gas chromatography-mass spectrometry (GC-MS), and antibacterial studies in the literature is presented to support these approaches.

2. Development and testing of antimicrobial strategies incorporating medicinal plant

Before plant extracts can be utilized, a meticulous process involving harvesting, pre-treatment, and various extraction methods must be followed to ensure the quality and efficacy of the final product. The initial step, harvesting, must be timed appropriately to capture the peak concentration of desired phytochemicals. Pre-treatment processes such as drying, grinding, and sometimes fermentation prepare the plant material for extraction, thereby enhancing the efficiency and yield of the subsequent steps. Different extraction methods, such as maceration, infusion, decoction, and modern techniques like supercritical fluid

extraction, are selected based on the chemical nature of the target compounds and their intended applications. The choice of solvent – whether organic, inorganic, or a combination of solvents – plays a critical role in selectively isolating specific phytoconstituents. Once extracted, these compounds often require further purification through techniques like chromatography to isolate the compound of interest, ensuring that the final product is potent and suitable for its intended use. This comprehensive approach ensures that plant extracts used in various applications, from pharmaceuticals to nutraceuticals, are both effective and safe.²³⁻²⁵

2.1. Strategy 1

A single plant extract or a combination of plant extracts can undergo chemical reactions by adding reagents such as organic or inorganic acids, alkalis, or catalysts while modifying the reaction conditions (e.g., temperature, pressure). A study by Gideon²⁶ exemplified this synergistic strategy by combining plant extracts with antibiotics to combat AMR. In the experiment, 0.4 mL of concentrated sulfuric acid was added to 10 mL of aqueous *Psidium guajava* (guava) leaf extract. The mixture was boiled at 100–110°C for 30 min, followed by centrifugation. The antimicrobial analysis revealed that untreated guava extract (at 5.0 µg/mL) had no inhibition zones against *Salmonella* spp., *E. coli*, *Streptococcus* spp., and *Staphylococcus aureus*. However, the 0.4 mL acid-treated guava extract (at 0.1 µg/mL) showed inhibition zones for all four bacterial strains, ranging from 7 mm to 12 mm, as depicted in Figure 1. The clear zones of inhibition in

Figure 1 were primarily observed in the acid-treated plant extract combined with the antibiotic.

ATR-FTIR analysis, as depicted in Figure 2 and Table 1, revealed significant changes in the peaks present in each sample. The unreacted extract displayed 14 peaks, while the reacted extract showed 10 peaks. Shift in peaks, the formation of new peaks, and a decrease in transmittance were observed. A decrease in transmittance is attributed to higher concentrations of compounds with certain functional groups, while the emergence of new peaks may be due to the formation of new or analogous compounds.²⁶ On centrifugation and drying at room temperature, the unreacted guava extract yielded a total mass of 13.7 mg, whereas the reacted guava extract yielded 177.2 mg, which is 1,293.4 times heavier than the unreacted guava extract. This significant difference in mass is attributed to the formation of larger and more complex molecules, which typically have higher molar masses.²⁷

Further exploration of this approach could involve isolating specific phytoconstituents and then initiating reactions between non-bioactive constituents of one plant extract and bioactive constituents of another, or between different solvent extracts (e.g., chloroform or n-hexane) from various plants. Multiple combinatorial reactions can be designed and executed based on expected outcomes.

Plant extracts also play a key role as capping and stabilizing agents in nanoparticle synthesis.²⁸ Saddaf *et al.*²⁹ synthesized silver nanoparticles (AgNPs) using aqueous root extracts from four medicinal plants and tested their antimicrobial efficacy on six different bacteria strains.



Figure 1. Antibacterial activities of the prepared samples against resistant bacteria. Image reproduced with permission from Gideon.²⁶

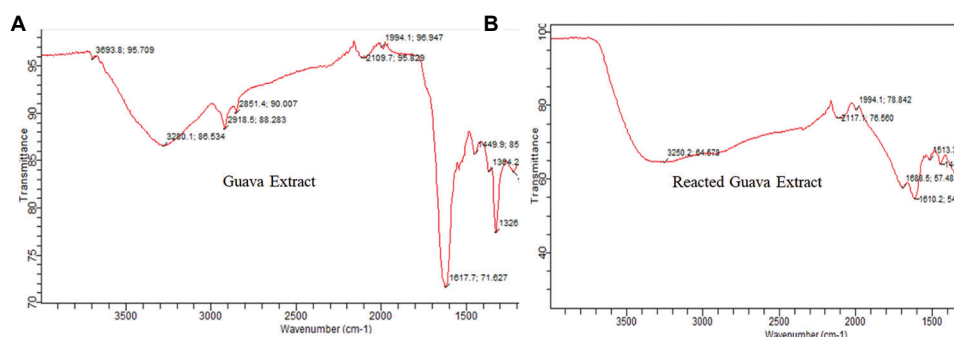


Figure 2. Attenuated total reflectance-Fourier transform infrared spectroscopy spectra of guava extract (A) and reacted guava extract (B). Image reproduced with permission from Gideon.²⁶

Table 1. Fourier transform infrared spectroscopy analysis of guava extract and reacted guava extract, including attributed functional groups. Reproduced with permission from Gideon²⁶

FTIR functional group region	Wavenumber range (cm ⁻¹)	Guava extract peaks (cm ⁻¹)	Reacted guava peaks (cm ⁻¹)	Associated phytochemicals
O-H/N-H Stretch	3,200–3,600	3,693.8; 3,280.1	3,250.2	Alcohols, phenols, amines, or carboxylic acids
C-H Stretch	2,850–3,000	2,918.5; 2,851.4	-	Alkanes
Alkanes Stretch	2,100–2,260	2,109.7; 1,994.1	2,117.1; 1,994.1	Alkynes or nitriles
C=O Stretch	1,630–1,820	1,617.7	1,688.5; 1,610.2	Ketones, aldehydes, esters, or carboxylic acids
N-H Bending	1,500–1,600	-	1,513.3	Primary and secondary amines
C-H Bending	1,400–1,500	1,449.9	1,442.5	Aromatic compounds

Abbreviation: FTIR: Fourier transform infrared spectroscopy.

Saddaf *et al.*'s results showed that the root extracts of *Bergenia ciliata* and *Bergenia stracheyi* (at 1200 µg/well) and their synthesized AgNPs (at 150 µg/well) did not inhibit the growth of *E. coli*, *Staphylococcus haemolyticus*, or *Bacillus cereus*. In contrast, the root extracts of *Rumex dentatus* and *Rumex hastatus* (at 1200 µg/well) were unable to inhibit these bacteria, but their synthesized AgNPs (at 150 µg/well) successfully inhibited bacterial growth. According to Saddaf *et al.*²⁹ (p321), "the antibacterial activity of each type of AgNPs depends on the surface modification by plant extract, which makes them effective against specific bacteria." In response to this statement, it can be argued that if the modification occurred on AgNPs themselves, rather than on the plant extract, lower levels of inhibition would have been observed in *B. ciliata* and *B. stracheyi* due to the contributory effect of silver's inherent antimicrobial activity. Instead, it is the modification of the phytoconstituents in these aqueous root extracts that promotes antimicrobial functionality, as demonstrated by Gideon.²⁶

2.2. Strategy 2

This strategy involves initiating a reaction between a single plant extract and an ineffective drug, known for treating the disease of interest. The process includes adding a reagent

– such as an inorganic/organic acid, alkali, or catalyst – and modifying the reaction conditions. For antibacterial applications, multiple plant extracts can be reacted with different inexpensive antibiotics. The antibiotic must be confirmed to be ineffective against the target bacteria, as using an antibiotic that is fully effective against the bacteria of interest could reduce the effectiveness of the final product if structural changes are made. For example, Gideon and Ladan³⁰ achieved consistent synergistic effects preparing a mixture of (i) 1 mg/mL amoxicillin with aqueous leaf extract of *Calotropis procera*; (ii) 1 mg/mL ampicillin with aqueous leaf extract of *C. procera*; (iii) 100 µg/mL azithromycin with aqueous leaf extract of *C. procera*; and (iv) 100 µg/mL ampicillin with aqueous leaf extract of *C. procera*, and reacting each with concentrated sulfuric acid at 110°C for 20 min. Greater zones of inhibition were observed, as shown in Figure 3. The clear zones of inhibitions in Figure 2 predominantly reflect the acid-treated plant extract in combination with the antibiotics. This method increased the synergism of the plant extract-antibiotic combinations, enhancing their effectiveness from 33% (as reported by Eze *et al.*,³¹ Moussaoui and Alaoui,³² and Haq *et al.*³³) to 100% at 1 mg/mL.

In a follow-up study by Gideon *et al.*,³⁴ GC-MS analysis of combination (i) from Gideon and Ladan's study³⁰ was

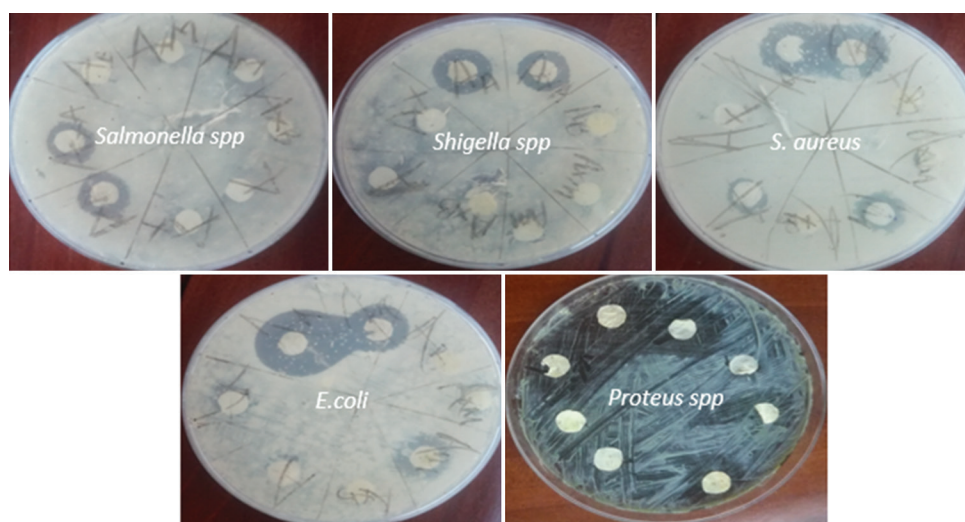


Figure 3. Antibacterial activities of prepared samples against resistant *Salmonella* spp., *Shigella* spp., *Staphylococcus aureus*, *Escherichia coli*, and *Proteus* spp. Image reproduced with permission from Gideon and Ladan.³⁰

carried out to investigate the transformations in both the phytoconstituents and the antibiotic that contributed to the observed synergistic activity. The clear inhibition zones in [Figure 3](#) primarily represent the acid-treated plant extract combined with the antibiotics.

The GC-MS analysis revealed 53 phytoconstituents, of which 18 were known for their biological activity, as shown in [Table 2](#). Three of these constituents – farnesol,³⁵ 4-amino-1-pentanol,³⁶ and an imidazole derivative resembling the drug ribavirin^{37,38} – were reported to have anticancer properties.

Further exploration can involve reactions between non-bioactive constituents from different plant extracts, the bioactive constituents of one plant combined with the non-bioactive constituents of another, chloroform extracts of various plants, or isolated compounds with n-hexane extracts. Multiple combinatorial reactions can be designed and carried out based on predicted outcomes.

2.3. Strategy 3

This strategy involves initiating a reaction between a plant extract and a drug not originally intended for treating the disease of interest, or any reagent suspected to possess good structural functionality that might enhance antimicrobial activities. Various methods can be employed while modifying the reaction conditions.

Gideon *et al.*³⁹ developed a regimen by making 24 different combinations of guava leaves and clove aqueous extracts with aspirin, tetracycline, and co-trimoxazole, each underwent different reaction stages. Antimicrobial susceptibility tests revealed that a single-stage combination

of co-trimoxazole with clove extract (Scl), a two-stage combination of aspirin and clove extract (Ac2), and a two-stage combination of aspirin and guava extract (Ag2) were all effective against the resistant isolates of *Salmonella* spp.

The antibacterial activity optimization of aqueous leaf extract of *P. guajava* against resistant clinical isolates of *S. aureus*, *E. coli*, *Streptococcus* spp., and *Salmonella* spp. was carried out by Gideon.²⁶ He added 4 mL of guava extract to 4 mL of aspirin solution, boiled the mixture in a water bath, then added 0.4 mL of sodium hydroxide and continued boil for 5 min. A fresh 2 mL portion of guava extract was added, followed by 0.3 mL of sulfuric acid, and the mixture was boiled for another 10 min before centrifugation. The antimicrobial activity is shown in [Figure 4](#).

The ATR-FTIR analysis revealed significant findings regarding the interaction between aspirin and *P. guajava*. From the ATR-FTIR results depicted in [Figure 5](#) and [Table 3](#), new peaks emerged in the combined product, including 3,235.3 cm⁻¹ (O-H stretching from guava extract), 2,918.5 cm⁻¹ (C-H stretching, alkanes from guava extract), 2,105.9 cm⁻¹ (C≡C stretching, alkynes from aspirin solution), 1,455.7 cm⁻¹ (C-H bending, alkanes from guava extract), 1,748.1 cm⁻¹ (C=O stretching, esters from aspirin solution), 1,677.3 cm⁻¹ (C=C stretching, alkenes from aspirin solution), 1,602.8 cm⁻¹ (C=C stretching, aromatics from aspirin solution), and 1,453.7 cm⁻¹ (C-H bending, alkanes from aspirin solution). These changes in peak positions and transmittance levels suggest significant structural modifications, with reduced transmittance indicating higher concentrations of compounds with specific functional groups.²⁶ The combined presence of peaks from both guava extract and aspirin solution

Table 2. Bioactive phytoconstituents from *Calotropis procera* leaf extract combined with ampicillin. Reproduced with permission from Gideon *et al.*³⁴

Pk#	RT	Area%	Compound name	Molecular weight
1	5.318	3.35	Cystamine	152.0
3	5.528	2.46	4-amino-1-Pentanol	103.0
5	5.959	1.42	N-methoxy-1-ribofuranosyl-4-imidazolecarboxylic amide	155.0
6	6.275	0.73	1,2,5-oxadiazol-3-carboxamide, 4,4'-azobis-, 2,2'-dioxide	284.0
9	7.361	1.94	3,3-dimethyl-4-(1-aminoethyl)-Azetidin-2-one	142.0
11	7.891	1.37	5-methyl-2-Heptanamine	128.0
20	12.065	1.36	dl-phenylephrine	167.0
23	14.598	1.16	Cystine	240.0
32	21.074	2.03	1,2,5-oxadiazol-3-carboxamide, 4,4'-azobis-, 2,2'-dioxide	284.0
34	22.127	0.73	Metaraminol	167.0
38	25.796	2.83	3-propoxyamphetamine	193.0
43	29.445	0.12	Hexadecanoic acid, methyl ester	270.0
49	30.437	2.68	1-docosene	308
50	31.083	0.16	9-octadecenoic acid (Z)-, methyl ester	296.0
52	36.087	0.78	3,7,11-trimethyl-2,6,10-dodecatrien-1-ol	222.0
53	36.620	13.04	Oleic acid	264.0

Abbreviations: Pk#: Number of peaks; RT: Retention time.

Table 3. Fourier transform infrared spectroscopy analysis of guava extract, aspirin, and the guava-aspirin mixture, with attributed functional groups. Reproduced with permission from Gideon²⁶

FTIR functional group region	Wave number range (cm ⁻¹)	Guava extract peaks (cm ⁻¹)	Aspirin peaks (cm ⁻¹)	Reacted guava peaks (cm ⁻¹)	Associated phytochemicals
O-H/N-H stretch	3,200 – 3,600	3,693.8; 3,280.1	3,488.8	3,235.3	Alcohols, phenols, amines, or carboxylic acids
C-H stretch	2,850 – 3,000	2,918.5; 2,851.4	2,870.1; 2,959.5; 2,698.6; 2,586.8; 2,545.8	2,918.5	Alkanes
Clkanes stretch	2,100 – 2,260	2,109.7; 1,994.1	2,091.0	2,105.9	Alkynes or nitriles
C=O stretch	1,630 – 1,820	1,617.7	1,804.0; 1,837.6; 1,751.8; 1,684.3; 1,602.8	1,748.1, 1,677.3, 1,602.8	Ketones, aldehydes, esters, or carboxylic acids
N-H bending	1,500 – 1,600	-	-	-	Primary and secondary amines
C-H bending	1,400 – 1,500	1449.9	1483.5; 1457.4	1453.7	Aromatic compounds

Abbreviation: FTIR: Fourier transform infrared spectroscopy.

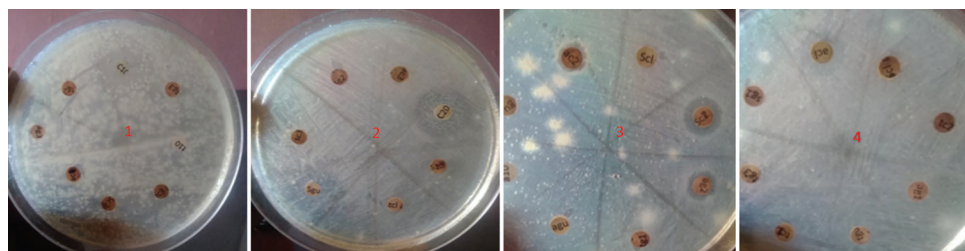


Figure 4. Antimicrobial susceptibility test for 31 prepared disks against *Salmonella* spp. Image reproduced with permission from Gideon *et al.*³⁹

confirmed the formation of a new compound with modified structural characteristics, suggesting that the

combination of aspirin with guava extract may lead to a novel product with enhanced antibacterial properties. This

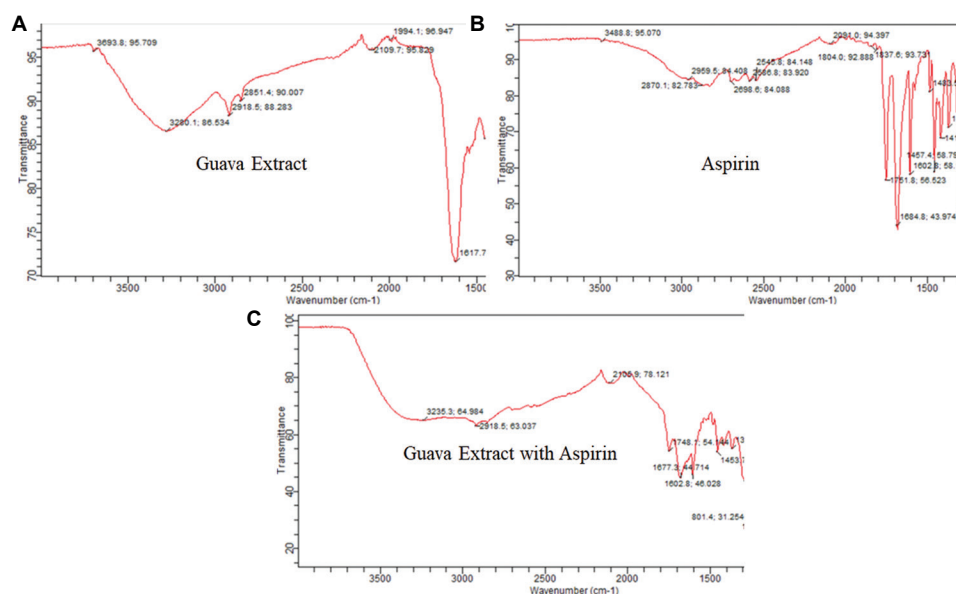


Figure 5. Attenuated total reflectance-Fourier transform infrared spectroscopy spectra of guava extract (A), aspirin (B), and guava-aspirin mixture (C). Image reproduced with permission from Gideon.²⁶

method can be further explored by reacting non-bioactive constituents of one plant extract with those of another, bioactive constituents of one plant with non-bioactive constituents of another, or using different solvents and isolated compounds. Various combinatorial reactions can be designed to achieve the desired outcomes.

3. Conclusion

This review outlines strategies for leveraging plant extracts in the fight against drug resistance. Functional group analysis, GC-MS data, and antimicrobial screenings from various sources demonstrate that combining plant extracts with drugs or other structurally functional reagents can induce significant structural and functional changes, resulting in the formation of intermediate or new compounds. These compounds may act individually or synergistically to combat multi-drug-resistant bacteria. For instance, the GC-MS analysis identified potent anticancer properties, suggesting that these combinations may also offer therapeutic potential in antifungal, anti-inflammatory, antiviral, and anticancer applications, potentially yielding positive outcomes similar to the observed antibacterial effects. Therefore, this approach holds significant promise and warrants further exploration using advanced synthetic methods and tools to optimize drug discovery and development. By harnessing the potential of plant extracts and employing sophisticated techniques, we can develop novel treatments to effectively address the growing challenge of drug resistance.

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