Chemical profiling of a polyherbal formulation by tandem mass spectroscopic analysis with multiple ionization techniques

Sulaiman C. T. 1*, Ramesh P. R. 2, Mahesh K. 2, Madhu K. M. 3, Anandan E. M. 4, Praveen M. 3 and Indira Balachandran 1

Abstract

Background: Gugguluthiktham Kashayam (GTK) is the decoction form of Panchatikta Guggulu Ghrita, a classical Ayurvedic formulation used for treating various diseases like skin disorders, ulcers, sinus, asthma, cardiac diseases, arthritis, and cancer.

Results: Tandem mass spectroscopic analysis of GTK was carried out by different ionization techniques such as electro spray ionization (ESI) and atmospheric pressure chemical ionization (APCI) in both positive and negative modes using Quadrupole Time-of-Flight (Q-TOF) mass spectroscopy. Data processing of molecular ions obtained by ESI and APCI mass fragmentation led to the identification of several phytoconstituents belonging to various classes of compounds such as phenolics, flavonoids, and coumarins.

Conclusion: The study concluded that GTK contains variety of phytochemicals with numerous biological properties that might be responsible for its various therapeutic effects.

Keywords: Gugguluthiktham Kashayam, Herbal formulation, ESI, APCI, LCMS

Background

Indian traditional medicines such as Ayurveda, Unani, and Siddha, have been practiced by billions of people for many centuries. Ayurvedic formulations contain multiple botanicals as ingredient materials some may be made with minerals, metals, and ingredients of animal origin, and each of these comprises a number of chemical compounds that may give the anticipated activity in combination. Polyherbal formulations show high effectiveness due to the presence of active phytochemicals that are further potentiated with synergetic interaction of active components of ingredient plants. GTK is the decoction form of Panchatikta Guggulu Ghrita, a classical Ayurvedic formulation used for treating various disease conditions including skin disorders, ulcers, sinus, asthma, cardiac diseases, arthritis, and cancer [1–3].

Liquid chromatography-tandem mass spectrometry has become the best method for separation, identification, and characterization of active constituents of herbal products and had a significant impact on drug development over the past decade. Continual improvements in LC/MS interface technologies combined with powerful features for structure analysis, qualitative and quantitative, have resulted in a widened scope of application, especially natural products. The advancement of multiple ionization techniques for the characterization of unknown samples has been reported earlier [4, 5].

Although research on Ayurveda has become a popular trend now, only a very small percentage of Ayurvedic medicines have been investigated targeting on their chemical components and biological activities. There are still a huge number of Ayurvedic preparations that are not investigated chemically. Most of the Ayurvedic classical
Table 1 ESI-LC-MS/MS analysis of GTK

| Sl no. | m/z       | MS/MS         | Tentative identification          | Type of compound | Molecular formula | Ionization mode |
|-------|-----------|---------------|------------------------------------|------------------|-------------------|-----------------|
| 1     | 191.0568  | 173.10        | Quinic acid                        | Phenolics        | C_{7}H_{11}O_{6}  | Negative        |
| 2     | 197.1452  | 179.02, 135.12| Syringic acid                      | Phenolics        | C_{9}H_{10}O_{5}  | Negative        |
| 3     | 153.0260  | 109.24        | Protocatechuic acid                | Phenolics        | C_{7}H_{6}O_{4}   | Negative        |
| 4     | 153.0256  | 109.03        | 2,5-Dihydroxybenzoic acid          | Phenolics        | C_{9}H_{10}O_{4}  | Negative        |
| 5     | 169.015   | 125.02        | Gallic acid                        | Phenolics        | C_{9}H_{6}O_{5}   | Negative        |
| 6     | 133.0179  | 115.23        | Malic acid                         | Phenolics        | C_{4}H_{6}O_{5}   | Negative        |
| 7     | 305.0386  | 225.02        | Gallo catechin                     | Catechin         | C_{15}H_{14}O_{7} | Negative        |
| 8     | 343.2245  | 299.25        | Anacardic acid (15:2)              | Phenolics        | C_{22}H_{32}O_{3} | Negative        |
| 9     | 341.2087  | 292.28        | Anacardic acid (15:3)              | Phenolics        | C_{22}H_{32}O_{3} | Negative        |
| 10    | 345.2314  | 301.26        | Anacardic acid (15:1)              | Phenolics        | C_{22}H_{32}O_{3} | Negative        |
| 11    | 353.1289  | 191.05, 179.12| Caffeoylquinic acid                | Phenolics        | C_{16}H_{18}O_{9}| Negative        |
| 12    | 355.023   | 337.02, 249.05| Chebulic acid                      | Phenolics        | C_{16}H_{18}O_{9}| Negative        |
| 13    | 463.0288  | 301.04        | Quercetin hexoside                 | Flavonoid        | C_{21}H_{20}O_{12}| Negative        |
| 14    | 289.0068  | 245.01        | Catechin                           | Phenolics        | C_{15}H_{14}O_{6} | Negative        |
| 15    | 297.154   | 183.01        | Cardanol                           | Phenolics        | C_{15}H_{14}O_{6} | Negative        |
| 16    | 173.0491  | 155.03, 137.02| Shikimic acid                      | Phenolics        | C_{7}H_{10}O_{5}  | Negative        |
| 17    | 179.0777  | 162, 135.08   | Caffeic acid                       | Phenolics        | C_{10}H_{10}O_{4} | Negative        |
| 18    | 237.0538  | 193.06        | 6-Hydroxy flavone                  | Flavonoid        | C_{15}H_{14}O_{5} | Negative        |
| 19    | 163.0499  | 119.05        | 2-Coumaric acid                    | Phenolics        | C_{6}H_{12}O_{5}  | Negative        |
| 20    | 193.0913  | 149.10        | Ferulic acid                       | Phenolics        | C_{10}H_{10}O_{4} | Negative        |
| 21    | 447.0657  | 300.16        | Quercetin-3-rhamnoside             | Flavonoid        | C_{31}H_{52}O_{11}| Negative        |
| 22    | 371.037   | 353.02, 191.02| 2-O-cafeoylglucaric acid           | Phenolics        | C_{15}H_{16}O_{11}| Negative        |
| 23    | 477.0594  | 301.14        | Quercetin-3-glucuronide            | Flavonoid        | C_{31}H_{52}O_{11}| Negative        |
| 24    | 255.254   | 209.12        | 2′,6-Dihydroxyflavanone            | Flavonoid        | C_{15}H_{16}O_{4} | Negative        |
| 25    | 610.1259  | 464, 302      | Rutin                              | Flavonoid        | C_{31}H_{52}O_{16}| Positive        |
| 26    | 757.718   | 301.14        | Quercetin-3-rhamnosyl glucoside    | Flavonoid        | C_{31}H_{52}O_{20}| Positive        |
| 27    | 449.427   | 287.26        | Kaempferol 7-O-glucoside           | Flavonoid        | C_{31}H_{52}O_{11}| Positive        |
| 28    | 271.257   | 253.36, 225.17| Apigenin                           | Flavonoid        | C_{31}H_{52}O_{16}| Positive        |

Fig. 1 ESI-MS-base peak chromatogram of GTK in negative ionization
formulations are Polyherbal preparations and their unique processing methods turn the ingredients into very complex mixtures, from which the separation and identification of chemical components is very difficult. It will be very imperative in the future to gain a better understanding of the chemical basis of these medicines. The present study is focused on the chemical analysis of an Ayurvedic formulation using tandem mass spectroscopic investigation with multiple ionization techniques.

Methods
Preparation of GTK
GTK was prepared by the Product Development Department of Arya Vaidya Sala, Kottakkal, Kerala, India, as per the method of Ayurvedic Formulary of India [1] and was dried into powder form using vacuum evaporator. Ten grams of this was dissolved in LC/MS grade methanol and kept under refrigerator until LC/MS analysis.

Instruments and general chromatographic conditions
LC–MS/MS experiments were performed on Agilent 6520 accurate mass Q-TOF-MS coupled with Agilent LC 1200 equipped with Extend-C18 column of 1.8 μm, 2.1 × 50 mm. The MS analysis was performed using ESI and APCI ionization techniques in positive and negative mode. Mass spectral data analysis was done by Agilent molecular ion extraction algorithm. The general conditions for mass spectrometry were drying gas (nitrogen) flow 8 L/min; nebulizer pressure 40 psig; drying gas temperature 300°C; capillary voltage 3000 V; fragmentor volt 125 V; Oct RF Vpp 750 V. The injection volume was 20 μl.

Optimization of LC/MS method
After several trail injections, the best mobile phase was fixed as gradient of acidified methanol (A) and water (B) system for ESI ionization mode. Gradient elution was performed at a constant flow rate of 0.9 ml/min, with an
increase in the volume of B%; 2-20%, 4-30%, 8-40%, 10-50%, 12-40%, 15-50%. The mass fragmentation was performed with varying collision energy 4 V/100 DA with an offset of 6 V. For APCI ionization, the mobile phase was optimized as 0.1% ammonium formate in water (A) and acetonitrile (B) in a gradient elution by changing percentage of A; 2-30%, 4-40%, 8-50%, 10-60%, 12-50%, 15-40%. The mass fragmentation was performed with varying collision energy 4 V/100 DA with an offset of 8 V.

Results

Identification of compounds by ESI ionization

LC/MS analysis was carried out with ESI ionization in both positive and negative modes. The total ion chromatogram (TIC) was extracted to molecular ions with the Agilent Mass Hunter software. In negative mode, TIC showed 53 molecular ion peaks and based on the abundance 30 ions were further fragmented in auto ms/ms analysis with varying collision energy. TIC was extracted to base peak chromatogram (BPC) by Agilent molecular ion extraction algorithm. The consistency of fragments was confirmed by targeted ms/ms analysis with fixed collision energy based on the auto ms/ms analysis. The ESI-MS fingerprint of GTK in negative mode (Fig. 1, Table 1) presented the ions of m/z 191—quinic acid, m/z 197.1452—syringic acid, m/z 153.0260—protocatechuic acid, m/z 153.0256—2,5-Dihydroxybenzoic acid, m/z 169.015—gallic acid, m/z 133.0179—malic acid, m/z 305.0386—gallocatechin [6, 7]. Anacardic acids such as anacardic acid (15:1), anacardic acid (15:2), and anacardic acid (15:3) were identified with m/z 345.2314, 343.2245, and 341.2087 respectively [8, 9].

The fragmentation patterns of ions with m/z 353.1289, 355.023, 463.0288, 289.0068, 297.154, 173.0491, and 179.0777 are in consistent with that of caffeoylquinic acid, chebulic acid, quercetin hexoside, catechin, cardanol, shikimic acid, and caffeic acid when compared with that of previous reports [10–12]. Phenolics such as 6-hydroxy flavone (m/z 237.0538), 2-coumaric acid (m/z 163.0396), and ferulic acid (m/z 193.0396), quercetin-3-

### Table 2 APCI–LC-MS/MS analysis of GTK

| Sl no. | m/z       | MS/MS   | Tentative identification          | Type of compound | Molecular formula | Ionization mode |
|--------|-----------|---------|-----------------------------------|------------------|------------------|-----------------|
| 1      | 193.0566  | 133.03  | 7-Hydroxy-6-methoxy coumarin       | Coumarin         | C_{10}H_{10}O_{5} | Positive        |
| 2      | 177.1412  | 77.23   | 4-Methylumbelliferone              | Coumarin         | C_{10}H_{10}O_{3} | Positive        |
| 3      | 217.0593  | 202.02  | 5-Methoxy-6,7-furanocoumarin       | Coumarin         | C_{11}H_{12}O_{5} | Positive        |
| 4      | 163.0441  | 107.05  | 7-Hydroxyfuranocoumarin            | Coumarin         | C_{7}H_{6}O_{3} | Positive        |
| 5      | 219.2102  | 115.24  | 8-Acetyl-7-methoxyfuranocoumarin   | Coumarin         | C_{12}H_{12}O_{5} | Positive        |
| 6      | 163.0396  | 144.12  | p-cumaric acid                     | Phenolics        | C_{7}H_{6}O_{3} | Negative        |
| 7      | 187.210   | 167.08  | Azelaic acid                       | Carboxylic acid  | C_{12}H_{16}O_{4} | Negative        |
| 8      | 299.253   | 179.16  | Diosmetin                          | Flavonoid        | C_{16}H_{12}O_{6} | Negative        |
| 9      | 455.3528  | 438.20  | Betulonic acid                     | Phenolics        | C_{16}H_{18}O_{3} | Negative        |
| 10     | 431.0918  | 270.25  | Apigenin 7-O-glucoside             | Flavonoid        | C_{21}H_{20}O_{10} | Negative        |

Fig. 4 APCI-MS-base peak chromatogram of GTK in negative ionization
| Sl no. | Compounds identified from GTK | Pharmacological properties | Reference |
|-------|---------------------------|---------------------------|-----------|
| 1     | Quinic acid               | Anticancer, anti-inflammatory, neuroprotective, antioxidant | [19]       |
| 2     | Syringic acid             | Anticancer, anti-diabetic, anti-inflammatory, anti-microbial, hepatoprotective | [20, 21]  |
| 3     | Protocatechuic acid       | Anticancer, anti-diabetic, anti-ulcer, anti-inflammatory, analgesic, hepatoprotective | [22, 23]  |
| 4     | 2,5-Dihydroxybenzoic acid| Anti-inflammatory, anti-rheumatic, antioxidant | [24]       |
| 5     | Gallic acid               | Anticancer, antimicrobial, antioxidant, anti-inflammatory | [25]       |
| 6     | Malic acid                | Cardioprotective, antioxidant | [26]       |
| 7     | Gallo catechin            | Anticancer, anti-cholesterol, antioxidant | [27]       |
| 8     | Anacardic acid (15:2)     | Anticancer, anti-inflammatory, lipoygenase (LOX-1), xanthine oxidase, tyrosinase | [28]       |
| 9     | Anacardic acid (15:3)     | Anticancer, anti-inflammatory, lipoygenase (LOX-1), xanthine oxidase, tyrosinase | [28]       |
| 10    | Anacardic acid (15:1)     | Anticancer, anti-inflammatory, lipoygenase (LOX-1), xanthine oxidase, tyrosinase | [28]       |
| 11    | Caffeoylquinic acid       | Anticancer, anti-inflammatory, lipoygenase (LOX-1), xanthine oxidase, tyrosinase | [19]       |
| 12    | Chebulic acid             | Anti-diabetic, antioxidant, anti-angiogenic, anti-inflammatory | [29]       |
| 13    | Quercetin hexoside        | Antioxidant, anti-inflammatory | [30]       |
| 14    | Catechin                  | Anticancer, antioxidant, anti-inflammatory | [27, 31]  |
| 15    | Cardanol                  | Anticancer, anti-inflammatory | [28]       |
| 16    | Shikimic acid             | Antimicrobial              | [32]       |
| 17    | Caffeic acid              | Anticancer, antibacterial, antiviral activity, antioxidant, anti-inflammatory, anti-atherosclerotic, immunostimulatory, antidiabetic, cardioprotective, antiproliferative, hepatoprotective | [33]       |
| 18    | 6-Hydroxy flavone         | Antioxidant, analgesic     | [34]       |
| 19    | 2-Coumaric acid           | Anticancer, antimicrobial, antioxidant, anti-inflammatory, antiproliferative | [35]       |
| 20    | Ferulic acid              | Anticancer, antioxidant, anti-inflammatory | [30]       |
| 21    | Quercetin-3-rhamnoside    | Anticancer, antioxidant, anti-inflammatory, antiviral, cardiovascular, antimicrobial | [30, 31]  |
| 22    | 2-O-cafeoylglucaric acid | Antioxidant, anti-inflammatory | [35]       |
| 23    | Quercetin-3-glucuronide   | Antioxidant, anti-inflammatory | [34]       |
| 24    | 2′,6-Dihydroxyflavanone   | Antioxidant                | [34]       |
| 25    | Rutin                     | Anticancer, antioxidant, anti-inflammatory | [30, 31]  |
| 26    | Quercetin-3-rhamnosylglucoside | Antioxidant, anti-inflammatory | [31]       |
| 27    | Kaempferol 7-O-glucoside  | Anticancer, antioxidant, anti-inflammatory | [36]       |
| 28    | Apigenin                  | Anticancer, antioxidant    | [37]       |
| 29    | 7-Hydroxy-6-methoxycoumarin | Anticancer                | [38]       |
| 30    | 4-Methyllumbelliferone    | Anticancer, anti-inflammatory, antibacterial, antifungal, antiviral | [39]       |
| 31    | 5-Methoxy-6,7-furanocoumarin | Anti-inflammatory, antibacterial, antifungal, antiviral | [39]       |
| 32    | 7-Hydroxy coumarin        | Anticancer, anti-inflammatory | [39]       |
| 33    | 8-Acetyl-7-methoxycoumarin | Anticancer, anti-inflammatory | [39]       |
| 34    | p-Coumaric acid           | Anticancer, antimicrobial, antioxidant, anti-inflammatory | [35]       |
| 35    | Azelaic acid              | Anticancer, antityrosinase, antibacterial | [40, 41]  |
| 36    | Betulinic acid            | Anticancer, antioxidant    | [42]       |
| 37    | 5,7,3′-trihydroxy-4′-methoxylavone | Anticancer         | [43]       |
| 38    | Apigenin 7-O-glucoside    | Anticancer, antioxidant    | [37]       |
rhamnoside (m/z 447.0657), 2-O-caffeoylglucaric acid (m/z 371.037), quercetin-3-glucuronide (m/z 477.0594), and 2’,6-dihydroxy flavanone (m/z 255.245) were identified from GTK by comparing their mass fragments with that of reported values [13–16].

The ESI-MS fingerprint in positive mode (Fig. 2, Table 1) presented the ions of m/z 610.1259—rutin, m/z 757.718—quercetin-3-rhamnosyl glucoside, m/z 449.427—kaempferol 7-O-glucoside, and m/z 271.257—apigenin. The mass fragmentation patterns of these compounds have been reported previously [10–12].

Most of the compounds identified by ESI ionization mode are polyphenolics in nature. The characterization was carried out using both negative and positive modes; however, better fragments were obtained with negative mode. The use of ESI method as ionization source in the analysis of phenolic compounds has been reported earlier [11, 12, 17].

Identification of compounds by APCI ionization

The mass spectroscopic characterization of GTK was further done by APCI ionization method (Fig. 3, Table 2). In positive mode, APCI-MS fingerprint showed molecular ions with m/z 193.0566, 177.1412, 217.0593, 163.0441, and 219.2102 which were identified as 7-hydroxy-6-methoxy coumarin, 4-methylumbelliferone, 5-methoxy-6,7-furano-coumarin, 7-hydroxycoumarin, and 8-Acetyl-7-methoxy- coumarin based on the mass fragmentation pattern [18]. In negative ionization mode (Fig. 4, Table 2), compounds such as p-coumaric acid (m/z 163.0396), azelaic acid (m/z 187.210), 5,7,3’-trihydroxy-4’-methoxyflavone (m/z 299.253), betulinic acid (m/z 455.352), and apigenin 7-O-glucoside (m/z 431.0918) have been identified by comparing the mass fragmentation pattern of the same with earlier reports [19].

Discussion

Quadrupole time-of-flight mass spectrometry (Q-TOFMS) is an excellent technique to analyze chemical constituents of complex herbal preparations due to its accurate mass measurement, high resolution, and ion separation [15]. Quick data processing procedures and molecular ion extraction algorithm tools have been used to process huge raw data generated from multiple ionization mass analyses. These processed data were thereafter used successfully for correlating with their reported biological properties (Table 3). Most of the compounds identified from GTK are reported to possess various pharmacological activities such as anti-inflammatory, antioxidant, cardio protective, anticancer, anti-diabetic, and analgesic.

The correlation of the chemical structure of the identified compounds with their previously reported pharmacological activities showed that most of the compounds have anti-inflammatory, antioxidant, and anticancer properties. Indeed, there are many reports of phenolic compounds showing very effective antioxidant, anti-inflammatory, and anticancer activities [30, 31].

The metabolomic profiling of GTK depicted the presence of 38 compounds including 19 phenolics, 11 flavonoids, 5 coumarins, 2 catechins, and 1 dicarboxylic acid. These major phytoconstituents are mainly responsible in curing various diseases as they reported to possess numerous biological activities and out of these, 27 compounds are known for their anticancer activity (Fig. 5).

Conclusion

In this study a novel method has been developed based on tandem mass spectroscopy to identify the major components of a polyherbal formulation. Ayurvedic formulations are gaining great importance as a cure for several...
health problems and are getting global attention these days. The ingredient analysis of such herbal preparations is the need of both industry and scientific community to facilitate better understanding about their quality and therapeutic efficacy. The study concluded that GTK, an important Ayurvedic preparation, is a rich source of phytochemicals which are reported mainly for their anticancer, anti-inflammatory, anti-oxidant, and anti-diabetic properties.

Abbreviations
GTK: Gugguliphitkham kashayam; LC-MS/MS: Liquid chromatography-tandem mass spectrometry; ESI: Electro spray ionization; APCI: Atmospheric pressure chemical ionization; Q-TOF-MS: Quadrupole time-of-flight mass spectrometry; TIC: Total ion chromatogram

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Authors’ contributions
SCT: Designed and executed the work. Carried out the LC/MS analysis RPR: Participated in planning and edited the manuscript MK: Provided background data for the design of work IB: Participated in planning and edited the manuscript All authors have read and approved the manuscript.

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Competing interests
The authors declare that they have no competing interests.

Author details
1Centre for Medicinal Plants Research, Arya Vaidya Sala, Kottakkal, Kerala, India. 2Clinical Research Department, Arya Vaidya Sala, Kottakkal, Kerala, India. 3Cancer Clinic, Charitable Hospital, Arya Vaidya Sala, Kottakkal, Kerala, India. 4Product Development Department, Arya Vaidya Sala, Kottakkal, Kerala, India.

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