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Original Research Article

Unani concept of drug substitution (therapeutic interchange) and its validation on scientific parameters

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ABSTRACT

Background: Unani concept of therapeutic interchange, despite having immense practical aspect, has not been touched upon in a coherent way by most of the Unani scholars except Razi (Rhazes 865–925 AD), who took the concept plausibly and framed rules for alternate drug prescription at the time of unavailability of the drugs of choice.
Objective: The Unani concept of therapeutic interchange is based on similarity in action, temperament and physical properties of drugs mainly botanicals, which are already established and need no further discussion; however, phytochemistry has not been considered a basis for substitution. Therefore, objective of this study was evaluation of the concept on phytochemical parameters as actions of most drugs are due to phytoconstituents.
Material and methods: Classical Unani literature pertaining to therapeutic interchange and ethnobotanical literature for uses and phytoconstituents of three botanicals and their respective substitutes were reviewed. Ethnobotanical literature was collected from well known search engine *viz.*, PubMed, Google Scholar, Scopus and Science direct. In view of exploring the concept on scientific basis, physicochemical, phytochemical and analytical (HPLC, GC–MS) studies were also conducted.
Results: The study exhibited similarity in phytoconstituents in main and substitute botanicals with insignificant differences. Direct relation between doses, actions, intensity of actions, temperament and chemical constituents of main and substitute botanicals was observed.
Conclusion: The study, however, seemed to validate the concept on the basis of phytoconstituents, further pharmacological studies on the basis of properties and activities is required to strengthen the concept.

1. Introduction

Classical Unani medical literature brings about enormous level of logical and philosophical descriptions in certain basic principles, which are difficult to understand even for today's Unani fraternity and prove to be "all about Greek" for non Unani persons. Most Unani concepts become an arduous issue when discussed in scientific provisos. Many Unani concepts remained of archaic nature because of non availability of scientific paraphernalia for validation of concepts in the period when this medicine was taking shape. Therefore, this system of medicine is still relying on old principles that are unable to cope with the paradigm shift and need fresh explanation for making the concepts simple and rational. Flawed explanations have further narrowed down the clarity of many concepts. Fortunately, increasing level of understanding of facts has given expositions favorable turn and last few decades have witnessed attempts to explicate classical concepts on new parameters, which have paved way for inclusion of scientific knowledge to discuss these concepts. Beside, scientific studies have confirmed efficacy of many botanicals on phytochemical basis indicating that drugs having similar active constituents may exert similar pharmacological actions.

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Concept of *Abdal-e-Advia* (drug substitution) is an important facet of Unani pharmacotherapy. It deals with needs, principles and related aspects of drug substitution for therapeutic purposes. Unani scholars have suggested substitutes merely on the basis of clinical observations without considering phytochemistry. Despite being vital, concept of drug substitution has not been talked about adequately by most Unani scholars. Razi (865–925 AD) is the only person who has dealt with the concept in detail [1]. But, he has mentioned substitutes of 122 drugs in his book, *Kitab-al-Abdal* (book of substitutes). Avicenna (980–1037 AD), another genius, is too vigilant in suggesting substitutes of single drugs in his book, the Canon of Medicine. He has described substitutes of just 61 drugs from a long list of 781 drugs that have been described by him [2].

When, a drug is genuinely prescribed in leave of drug of choice, it is known as a substitute. Unani drugs are substituted when they are endangered, costly, rare, banned or the procurement cumbersome. A drug is prescribed as a substitute only for a particular action, as the substitute could differ from main drug in other actions. There are frequent examples of substitute between drugs of different origins, e.g., a botanical can be substitute of an animal or mineral origin drug. Furthermore, if a fresh drug is in short of availability, inferior quality of the same may be used in increased dose to maintain efficacy. Similarly, if a particular part of a botanical is not available; other parts of the same botanicals may be used [1].

As per the Unani concept, basis of substitution of drugs for therapeutic purposes are *Yaksaniyat-e-afal* (similarity in action), *Yaksaniyat-e-mizaj* (similarity in temperament) and *Yaksaniyat-e-zahiri khususiyat* (similarity in physical properties/organoleptic characters) of main and substitute drugs [1]. Accordingly, in case of non availability of intended drug, another drug having similar action or temperament or physical properties or any two or all is substantial for selection of a substitute [1]. *Badal* (substitution) may be *Badal-e-aqrab* (closest substitution) in which both drugs are similar in action, origin, and type, e.g., substitute of natural borax is artificial borax; *Badal-e-qareeb* (closer to substitution) in which both drugs are similar in action and origin, like ammonium chloride is therapeutic interchange of natural borax; *Badal-e-bayed* (remote substitution) in which both drugs are similar in action only, e.g., natural borax is substitute of black mustard. However, preference is given to similarity in action followed by origin and lastly type of drugs. When, main and substitute drugs are similar in all actions, practically rare, it is called *badal-e- kulli* (complete substitution), but when the drugs are similar in few actions, it is called *badal-e-juzwi* (partial substitution) [3].

Ayurveda classical texts have introduced "*abhava-pratinidhi dravya*" concept for therapeutic interchange [4]. In the absence of a desired first choice medicinal herb, classical Ayurveda recommends use of a functionally similar substitute [5]. As per the Ayurvedic concept of *abhava-pratinidhi dravya*, a rare or unavailable medicinal plant is substituted by a more readily available species [6]. However, the core concept of therapeutic interchange of Unani medicine and Ayurveda are similar but rules are different from each other.

2. Material and methods

The study reviews Unani literature pertaining to drug substitution, ethnobotanical literature for pharmacological activities and phytochemistry, and physicochemical and analytical studies to appraise the concept. Pharmacological activities and chemical constituents of all the six drugs were explored from well known scientific search engines *viz*., PubMed, Medline, Google Scholar, and Science Direct. Referred studies published in peer reviewed indexed journals were included. Classical Unani books were reviewed for Unani terms and selection of the test drugs. The literature from Unani medicine is cited as a reference wherever quoted. The key words used in classical books for the search of literature related to study are *Abdal-e-Advia*, *Badal*, *Badal-e-aqrab, Badal-e-bayed, badal-e- kulli, badal-e-juzwi, Badal-e-qareeb.*

From the list of commonly used Unani drugs, six important drugs having different actions like astringent, sedative and carminative were sorted out from classical Unani books. These drugs were divided in to three groups as: Group I: *Balaila* (*Terminalia belerica* (Gaertn.) Roxb.) named as TB and *Amla* (*Emblica officinalis* Gaertn.) named as EO were selected as main and substitute drugs, respectively (astringent); Group II: *Dhatura* (*Datura stramonium* Linn.) named as DS and its substitute *Ajwain Khurasani* (*Hyoscyamus niger* Linn.) named as HN were chosen as main and substitute drugs respectively(sedative); Group III: *Qaranful* (*Syzygium aromaticum* (Linn.) Merr. and L.M. Perry) named as SA and *Jaiphal* (*Myristica fragrance* Houtt.) named as MF were selected as the main and substitute drugs, respectively (carminative).

2.1. Plant material and preparation of extract

All test drugs were procured from local herbal drug market of Bengaluru and the samples were authenticated by Dr. S. Noorunnisa Begum, FRLHT (Foundation for Revitalization of Local Health Tradition), Bengaluru (certificate no. 3839, 3840, 3841, 3842, 3843 and 3844, respectively). Voucher specimens were kept at drug museum of National Institute of Unani Medicine (NIUM), Bengaluru. All chemicals used in this study were of analytical grade and were purchased from authentic suppliers. The drugs were crushed into small pieces by mortar and pestle and coarsely powdered in an electrical grinder; 100 g of each drug was extracted in petroleum ether, benzene, chloroform, acetone, ethanol and water in Soxhlets apparatus for 6 h for determining yield percentage and preliminary phytochemical studies. Extract were filtered by filter paper (Whatman no.40), the filtrate was concentrated till it dried completely [7].

2.2. Isolation of essential oils

Air-dried powder material (40 g) of crushed buds of SA and kernel of MF was extracted for 12 h (drug: water: 1:5) using Clevenger distillation apparatus. Oil part was carefully collected in a separated sealed container to avoid evaporation and preserved in a sealed vial at 4 °C till further analysis. Percentage yield was taken by the following formula (Naher et al., 2013).

$$\text{Yield } (\%) = \frac{\text{Amount of essential oil recovered (g)} \times 100}{\text{Amount of plant material used (g)}}$$

2.3. Physicochemical studies

Yield percentage (extractive value) was determined by the method given in British Pharmacopoeia [7]. Preliminary Phytochemical studies were carried out by the methods of Tarek et al., 2014; Bhattacharjee and Das, 1969) [8,9].

2.4. HPLC of ethanol extract of test drugs

Sample preparation

- Weigh accurately about 100 mg (Amla)/200 mg (Balela) Extract in to a 100 mL volumetric flask.
- And add 40 mL of Hot HPLC Grade water and sonicate for 10 min
- Cool and make up the volume to 100 mL with HPLC Grade Water.
- Mix well and filter the solution through 0.2μm (or) 0.45μm membrane filter paper

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Procedure: Set the instrument as per the chromatographic condition as prescribed above. Inject 20 μL of standard preparation and record the chromatogram. Inject another 3 times and calculate the mean area and the RSD. The RSD should not be more than 2.0%. Inject 20 μL of sample preparation and record the chromatogram.

Calculations: Gallic acid and Ellagic acid using following formula.

$$\frac{\text{Area of the sample} \times \text{Weight of standard in mg} \times \text{Sample dilution} \times \text{Purity of standard}}{\text{Area of the standard} \times \text{Standard dilution} \times \text{Sample weight in mg}}$$

HPLC was run for quantitative estimation of gallic acid and ellagic acid in TB and EO and atropine in DS and HN. For this, ethanol extract was used. For gallic acid and ellagic acid, mobile phase was prepared by dissolving 0.136 g of anhydrous potassium dihydrogen orthophosphate in 900 ml of HPLC grade water and 0.5 ml of orthophosphoric acid to make 1000 ml, filtered through 0.45μ membrane and degassed in a sonicator for 3 min, and considered as solvent A. Acetonitrile acted as solvent B. Gradient conditions (time in minute) was 0.01, 18.0, 25.0, 28.0, 35.0, 40.0 and 45.0. Buffer concentration was 95.0, 80.0, 65.0, 65.0, 80.0, 95.0, 95.0 for solvent A and 5.0, 20.0, 35.0, 35.0, 20, 05.0, 5.0 for solvent B. Standard preparation was made by gallic acid 0.1 mg/ml in HPLC grade water and ellagic acid 0.1 mg/mL of ellagic acid in HPLC grade methanol. Sample was prepared accurately weighed 100 mg EO/ 200 mg TB extract in a 100 mL volumetric flask, added to this 40 ml of hot HPLC grade water and sonicated for 10 min, cooled and made up the volume to 100 mL with HPLC grade water, mixed well and filtered through 0.2μm membrane filter paper. Column was Hibar, prepacked column, Li Chrospher 100, RP-18e (5 μm) (Merck) Phenomenex- Luna 5μm C-18(2), size 250 × 4.60 mm, wave length 270 nm, flow rate 1.5 mL/min, Injection volume 20 μL standard preparation (20 μL) was injected and the chromatogram was recorded.

For Atropine, mobile phase was prepared by dissolving 0.377 g of anhydrous sodium dihydrogen phosphate in 210 mL of *milli Q* water, filtered through 0.45 μm membrane and degassed in a sonicator for 10 min, considered as solvent A. Methanol (280 mL) degassed in a sonicator for 10min was considered as solvent B. Acetonitrile (500 ml) degassed in a sonicator for 10 min was considered as solvent C. Standard preparation of atropine (Sigma, Purity of Atropine standard: 99% pure) was prepared by 1 mg/mL of atropine stock solution in ethanol and serial dilution made 0.1 mg/mL, 0.01 mg/mL and 0.001 mg/mL in 21% for solvent A, 28% for solvent B and 50% for solvent C. All the samples are diluted 1000 times by adding 1 μL of sample in 999 mL of mobile phase. Method was isocratic, time (minute) was 0 and 15, flow (mL/min) was 1.0, 1.0 for solvent A; 21, 21 for solvent B; 28, 28, for solvent C, 50, 50. Column was Syncronis C18 reverse phase column with Dim. 250 × 4, 6 mm with 5μ particle size, wave length was 200 nm–600 nm, flow rate as 1.0 mL/min. The entire standard prepared (10 μL) were injected and the chromatogram was recorded.

2.5. GC–MS (total ion chromatography) of ethanol extract and hydro distillate of test drugs

GC–MS was carried out on four samples for estimation of atropine and eugenol. Ethanol extract of DS (I) and HN (II) was used for atropine and hydro distillate of SA (III) and MF (IV) was used for eugenol. Sample I and II were prepared by diluting 10 times with methanol. Sample III and IV were prepared by diluting 1000 times with hexane. Instrument was GC, Agilent 7890A, and MS: 5975C MSD. Ionization for MS was Electron Impact Ionization; Mass Analyzer: Single Quadrupole; Column: DB 5 MS; Dimensions: 30 mL × 0.25 mm ID × 0.25um film thickness. Temperature ramp, initial (°C) 70. Hold time (min) 2. Ramp. Rate (°C/min), 5, 3, 10. Temperature (°C), 70,150,250,310. Hold time (min) 2,0,2,3. Software, AMDIS and NIST 2011. Carrier Gas, Helium. Flow (mL/min): 1.0. Mode, Split, Split ratio 25:1. Injection volume, 1.0 μL. Scan Mass range, 30 m/z–500 m/z. Mobile phase prepared by dissolving 0.251 g of anhydrous sodium dihydrogen phosphate in 150 mL of milli Q water, filtered through 0.45μm membrane and degas in a sonicator for 10 min known as solvent A. Methanol (200 mL) degassed in a sonicator for 10 min was solvent B. Acetonitrile (650 ml) degassed in a sonicator for 10 min -solvent C. Method, Isocratic. Time (minute) 0, 15. Flow (mL/minute) 1.0, 1.0. For solvent A, 15, 15, for solvent B, 20, 20, for Solvent C, 65, 65. Column Syncronis C18 reverse phase column with Dim. 250 × 4. 6 mm with 5μ particle size; Wave length, 290 nm, Flow rate 1.0 mL/min. Injection volume: 10 μL. Standard prepared by 0.1 M of Eugenol stock solution in Ethanol and serial dilution made 1000 μM, 100 μM, 10 μM,

Table 1
Pharmacological activities, qualitative and quantitative phytochemical analysis ethanolic extract of tested botanicals.

Botanicals	Pharmacological activities	Qualitative phytochemical estimation	Quantitative analysis of phytoconstituents
Terminalia belerica (Gaertn.) Roxb. and *Emblica officinalis* Gaertn.	Antioxidant [10], Wound healing [12,13], Analgesic [14], Antidiarrhoeal [12], Anti diabetic [11], Antipyretic [14]	Alkaloids, carbohydrates, glycosides, terpenes, phenols, flavonoides, proteins, fixed oils, tannins, diterpenes, quinines anthraquinones, coumarins	Gallic acid and Ellagic acid 2.5% in TB and 0.5% in EO
Datura stramonium Linn. and *Hyoscyamus niger* Linn.	Analgesic [14], Anti inflammatory [14,15], Antimicrobial [16,17,20], Sedative [18,19]	Alkaloids, glycosides, carbohydrates, fixed oils, flavonoides, phenols, tannins, coumarins, diterpenes, quinines, anthraquinones, saponins	Atropine 0.030567% in DS and 0.026470% in HN
Syzygium aromaticum (Linn.) Merr and L.M. Perry. and *Myristica fragrance* Houtt.	Antioxidant [19,21,22], Anti-inflammatory, Antimicrobial, Anti fungal [8,19,24]	Carbohydrates, terpenes, fixed oils, flavonoides, phenols, saponins, proteins, amino acids, coumarins, alkaloids, glycosides, diterpenes	Eugenol 2931.097 μmol in SA and 147.305 μmol in MF

TB, *Terminalia belerica* (Gaertn.) Roxb; EO, *Emblica officinalis* Gaertn; DS, *Datura stramonium* Linn; HN, *Hyoscyamus niger* Linn; SA, *Syzygium aromaticum* (Linn.) Merr. and L.M. Perry; MF, *Myristica fragrance* Houtt.

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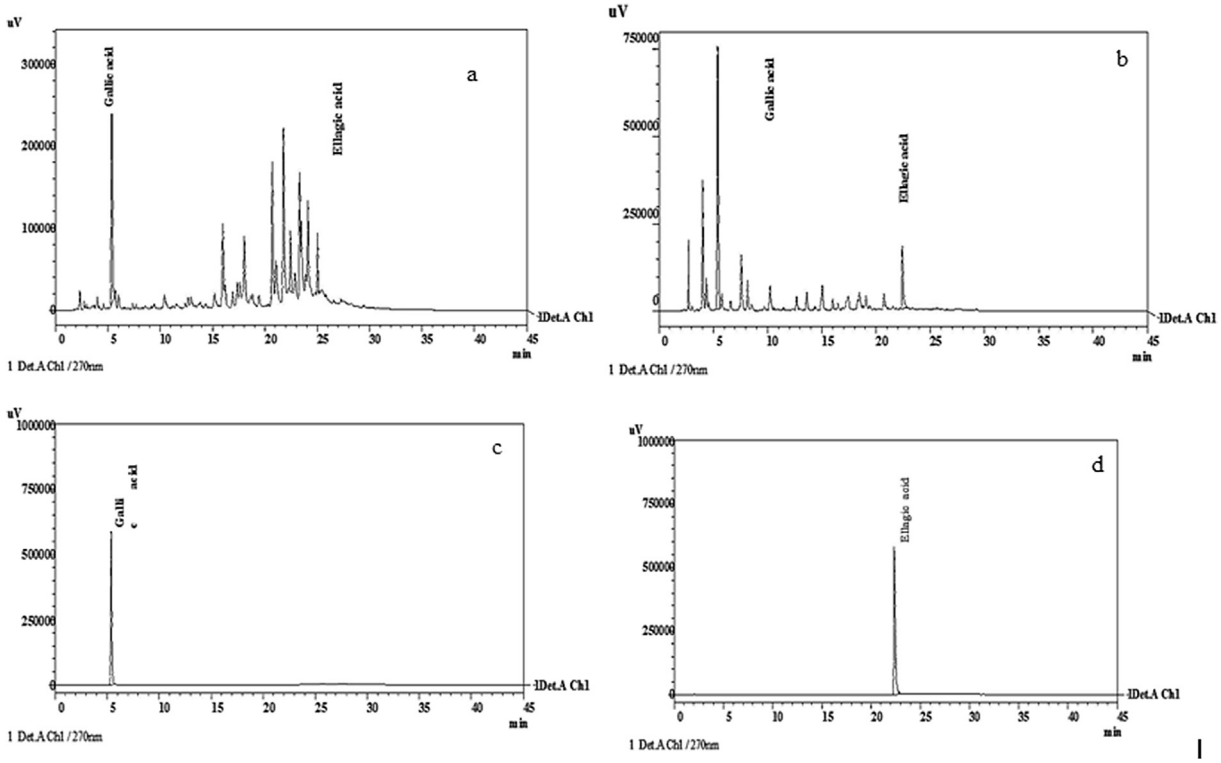

Fig. 1. HPLC chromatogram of Ethanoic extract (a) *Emblica officinalis*, (b) *Terminalia belerica*, (c) Gallic Acid and (d) Ellagic Acid.

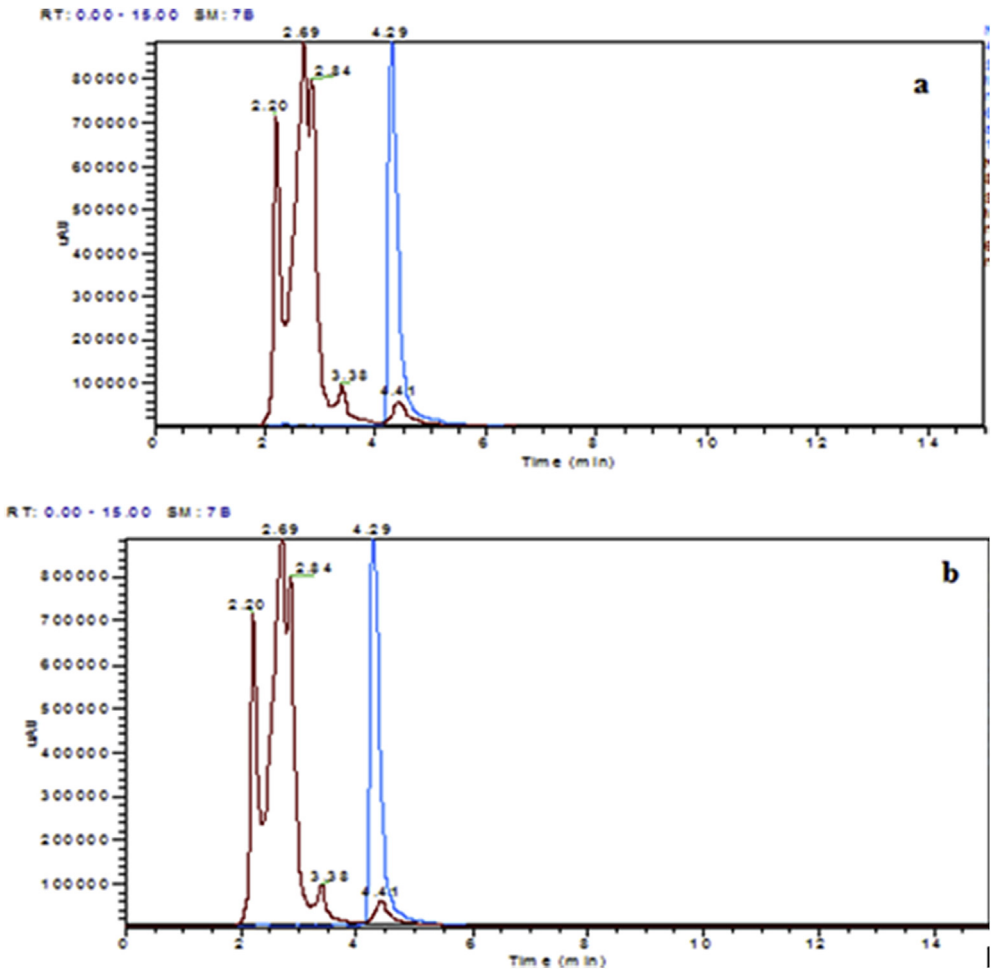

Fig. 2. HPLC chromatogram of (a) Atropine and *Hyoscyamus niger* and (b) Atropine and Datura stramonium.

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1 μM and 0.1 μM in 15% Solvent A, 20% Solvent B and 65% solvent C. All the samples were diluted 500 times by adding 2 μL of sample in 998 mL of mobile phase. The instrument was set as per the chromatographic condition described above. Injected 10 μL of the entire standard prepared and injected 10 μL of prepared samples.

3. Results

Ethnobotanical literature reveled most of the actions of main and the substitute drugs similar within the groups. Most of actions described in Unani medicine were also reported in ethnobotanical literature along additional actions (Table 1 and Figs. 1–4). Most of the chemical constituents of main and the substitute drugs were similar within the groups (Table 2).

3.1. Physicochemical studies

The yield percentage of TB, EO, DS, HN, SA, and MF determined in Petroleum ether, Benzene, Chloroform, Acetone, Ethanol, and Water were as 1.21, 0.42, 0.21, 0.10, 1.16, 0.31; 21.93, 24.43, 34.49, 20.42, 5.81, and 28.24**;** 35.16, 31.09, 2.14, 2.46, 0.73, 3.71; 2.34, 0.89, 7.09, 3.80, 8.35 and 9.24 respectively. The percentage yield of oil of SA and MF were 10% and 12.5% respectively.

3.2. Phytochemical studies

Results of qualitative phytochemical studies are mentioned in (Table 1).

3.3. HPLC and GC -MS of test drugs

In TB, gallic acid was found as 2.6%, but 5.6% in EO. Ellagic acid was 0.5% in TB but 1% in EO. The amount of atropine in DS was 0.030567 mg in 10 μL injection volumes and in HN it was 0.026470 mg in10 μL injection volume. Oil of SA and MF contained β-Thujene, β-Pinene, Sabinene. The amount of eugenol for SA oil was 2931 μmol in 10 μL injection volumes and in MF it was 147 μmol in 10 μL injection volumes as estimated by HPLC. Amount of eugenol estimated by GC–MS was found in negligible quantity (Table 1).

4. Discussion

Classical Unani concept of drug action and substitution has no room for phytochemistry. Though, it is magnanimity of Unani physicians who framed rules without any knowledge of phytochemistry. The study emphasized the core concept of drug interchange according to the guidelines mentioned in Unani literature. It tried to see agreement among the Unani rules of substitution through the similarity in drug action because of the chemical constituents present in the exemplified pair of drug and its substitute. According to Unani medicine, drugs act by *Mizaj* (temperament), *Maddah* (matter/physical properties/organoleptic characters) and *Surate nauiyah* (specific form/structure of drugs). Temperament and physical properties have already been considered as the basis of drug substitution [1], but not phytochemistry. Phytochemistry may be correlated with action of drug on the basis

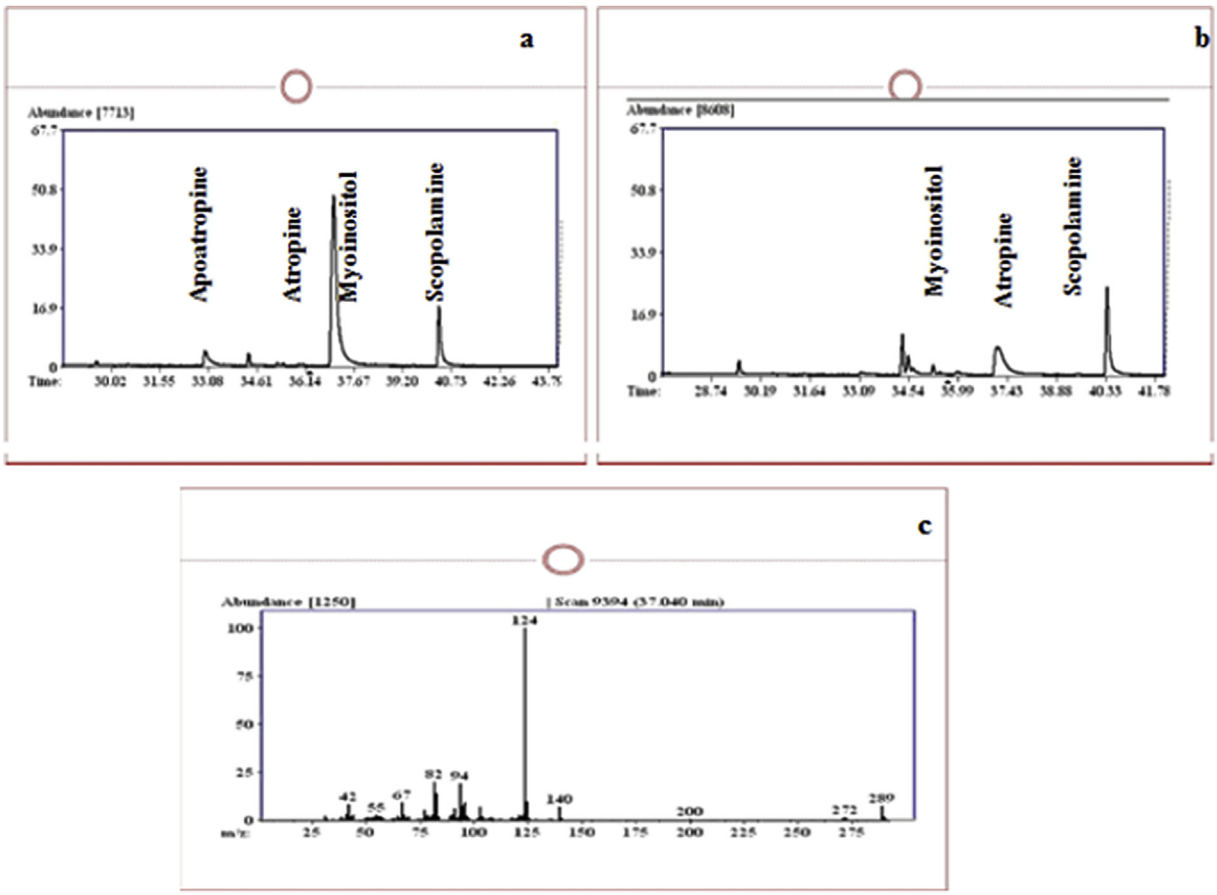

Fig. 3. GC–MS Total ion chromatogram of (a) *Datura,* (b) *Hyoscyamus* and (C) Atropine.

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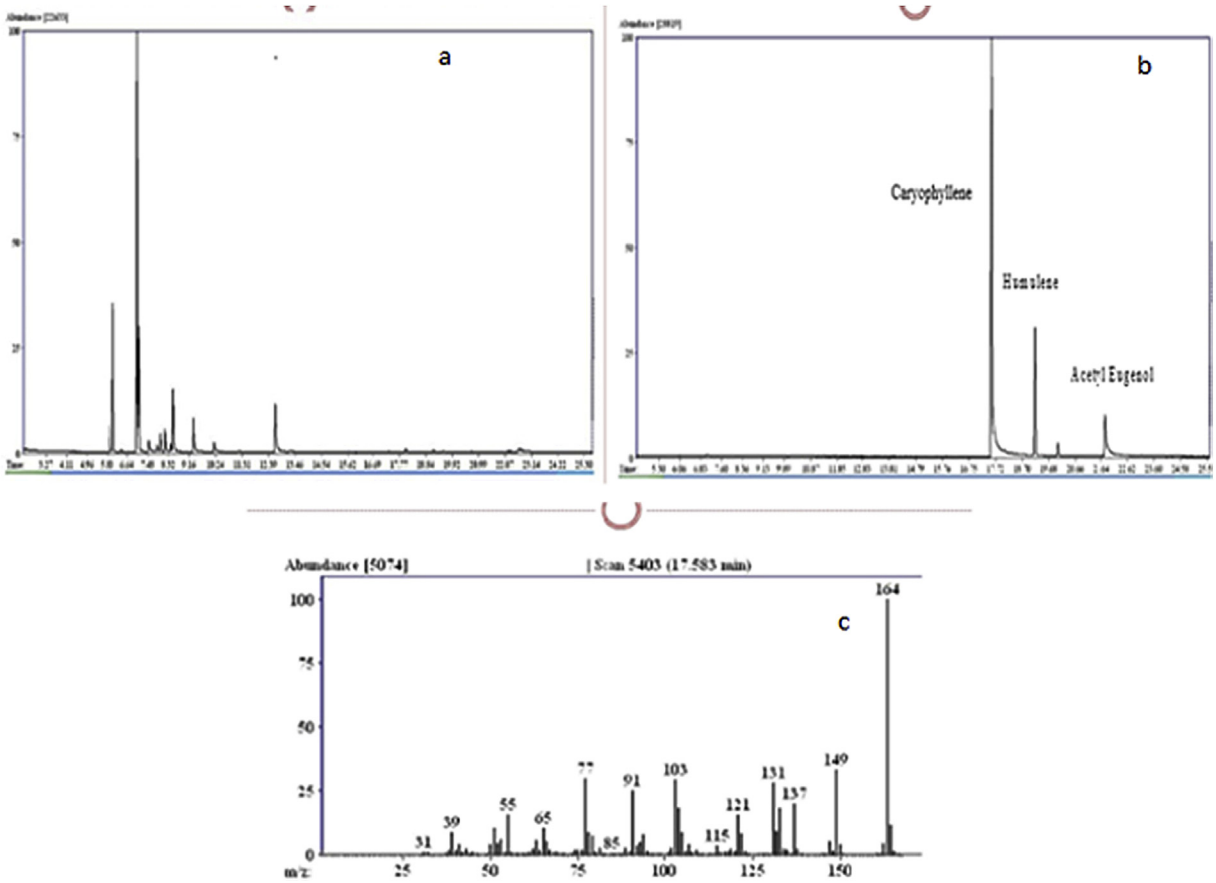

Fig. 4. GC–MS Total ion chromatogram of (a) Nut Meg oil, (b) Clove oil and (C) Eugenol.

of specific form because a drug becomes specific due to its chemical profile. If phytochemistry is considered as the basis of drugs' action, the concept might be furthered to a great extent because analogous chemical constituents in two drugs are reported to have similar actions. The same has also been established by literature and phytochemistry (Tables 1 and 2; Figs. 1–4).

Of the three central pedestals of substitution, similarity in action of main and substitute drugs is on top, which is supported by the literature. Second important base was temperament of drugs. If action of a drug is seen in the standpoint of phytochemistry, temperament of drugs can be attributed to the phytoconstituents because temperament and degrees of temperament, logical model to determine the action of a drug and intensity of action on a parametric scale [30], has been assigned to all Unani drugs. Overall, similarity in action should be considered as the key basis, but physical properties (Organoleptic characters) of drugs are considered third significant basis for substitution. Most Unani books have favored it. Organoleptic characters of crude drugs are important parameters of assuming actions of drugs. Unani physicians have postulated that drugs having similar taste, color, and odor may have similar actions. In Unani medicine, it is known as analogy, most part of which has been proved by experimentation [31]. Extractive values that represent primary and secondary constituents of crude drugs can be ascribed to these characters.

Astringent drugs contain gallic acid/ellagic acid (tannins) [28]. We found tannins in both astringent drugs. Tannins are the main constituents determining degree of astringency in fruits. It is reported that higher the tannin concentration, more is bitterness and astringency of the drugs [32]. We found atropine, hyoscyamine and scopolamine to be common in DS and HN both. HPLC also confirmed the same. These alkaloids induce sleep and are thought to be useful in the treatment of insomnia [33]. Likewise, essential oil was common in the two carminative drugs. GC–MS also confirmed the same. SA and MF contained β-Thujene, β-Pinene and Sabinene. Flatus is formed mostly as a result of microbial action on food. Essential oils have been believed to be digestive and

Table 2
Chemical constituents of the botanicals as reported in ethnobotanical literature.

Main drugs	Substitute drugs
Terminalia belerica (Gaertn.)Roxb.	*Emblica officinalis* Gaertn.
Gallic acid, tannic acid, glycosides, inorganics	Ascorbic acid and gallo tannins, tamlic acid, corilogin
Datura stramonium Linn.	*Hyoscyamus niger* Linn.
Hyoscyamine, hyoscine, atropine, fixed oil	Hyoscyamine, atropine belladonine, scopoletin, hyoscine, pyridine.
Syzygium aromaticum (Linn.) Merr. and L.M. Perry.	*Myristica fragrance* Houtt.
β-Thujene, β-Pinene, Sabinene, Eugenol, Caryophyllene, Humulene, Acetyleugenol.	β-Thujene, à-Pinene, Sabinene, á-Pinene, á-Myrceneà,- Phellandrene, 3-Careneα-, Terpinene, m,-Cymene, D-Limonene, L-β-Pinene, Terpinene Terpinolene, Terpinen-4-ol, Copaene

Source: [23], [25–29].

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carminative [34] and have also been screened for their antibacterial activity [35]. Qualitative estimation of chemical constituents is better than physicochemical standards, but not sufficient enough unless estimated quantitatively. For this reason, HPLC and GC–MS were carried out. Gallic acid and ellagic acid, atropine and eugenol were used as marker for TB, EO; DS HN and SA and MF, respectively.

Unani physicians have categorized drugs into four groups with reference to the effect on human body as hot, cold, wet and dry and combination of two with four degrees as 1st, 2nd, 3rd, or 4th for describing intensity of action. More is the degree of temperament; intense is the action [31]. If character and amount of active principles is deemed responsible for action, we may conclude degrees of temperament to be responsible for intensity of action. In a literary study, the authors tried to find out relationship between chemical constituents, and temperament with reference to taste of the drugs. Of selected 100 drugs, they found 80% drugs hot, 17% cold, and 3% balanced. Of hot and dry drugs, 40% percent contained alkaloids and 58% glycosides. Hot and moist drugs were composed of fixed oil, essential oil, phenol, resin, and saponins in traces. Of cold and dry drugs, 80% contained tannin. Cold and moist drugs contained alkaloids, fat, fixed oil and essential oil in traces. Alkaloid and glycoside bearing drugs were found having higher degree of temperament and thereby potent [36]. Thus, chemical constituents and temperaments had direct relationship with actions. This study further put right the idea of considering phytochemistry as the basis of drug substitution.

When temperament of TB and EO was compared, it was found that TB is $cold^2$ dry^2 and EO is $cold^2$ dry^3 [31]. In this outlook, correlation becomes apparent as greater amount of gallic acid and ellagic acid in EO makes it more astringent and thereby degree of temperament is also high. EO is comparatively more acerbic due to this reason [31]. Unani physicians have also considered dose of drugs while suggesting substitutes [31]. Atropine and hyoscyamine are mainly responsible for the action of DS and HN. When, we compared doses of DS and HN, ample difference was noted. DS contains more atropine than HN. Dose of DS is 500 mg whereas that of HN is 500–1250 mg, also temperament of DS is $cold^4$ dry^4 whereas that of HN is $cold^3$ dry^3[31]. These characteristics make DS more potent. Eugenol is responsible for carminative action; therefore, it was taken as marker for SA and MF. Tempting findings were obtained again. The amount of oil in SA was found more than MF. This finding also correlates dose and temperament as dose of SA is 3.5–4.5 gm whereas that of MF is 4.5–9 g, and temperament of SA is hot^3 dry^3 where as that of MF is hot^2 dry^2 [31]. Since, SA is relatively less potent; therefore, its dose is less than MF. Hence, relation between phytoconstituents, dose and temperament of drugs seemed justified. Above data are salient examples of correlation and are more explanatory and strongly support our hypothesis for taking phytochemistry as the basis of action and substitution than Unani concept alone.

5. Conclusion

The study validated Unani concept of drug substitution for three pairs of drugs of choice and the substituted drugs and augmented it with evidences from phytochemistry that provides a lead for searching new substitutes for herbal drugs and opens avenues for substituting drugs which are rare or becoming extinct and safer and cheaper substitutes for toxic, expensive and rare drugs. However, similarity in action will remain the most important basis irrespective of temperament, physical properties and phytochemistry. Such examples are frequently seen in conventional medicine where entirely different drugs are used for the same effect.

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Conflict of statement

Authors declare no conflicts of interest.

References

[1] Razi Z, Abdal Kitab Al, editors. New Delhi: CCRUM, ministry of health and family welfare, govt. of India. 3rd ed. 2000.
[2] Sina I. New Delhi: Idara Kitabus Shifa; YNM. In: Al qanoon fil tib. (Urdu translation by kanturi G). vol. 2; 2007. p. 1–1568.
[3] Qureshi H. Muqadma ilmul advia. New Delhi: Aijaz Publishing House; 1995.
[4] Nagarajan M, Kuruvilla GR, Kumar KS, Venkata subramanian P. Pharmacology of *Ativisha, Musta* and their substitutes. J Ayurveda Integr Med 2015;6(2):121–33.
[5] Nagarajan M, Kuruvilla Gina R, Subrahmanya Kumar K, Padma Venkata subramanian. *Abhava pratinidhi dravya*: a comparative phytochemistry of *Ativisha,* Musta *and related species*. J Ayurveda Integr Med 2015;6(1):53–63.
[6] Venkata subramanian P, Kumar SK, Nair VS. Yperus rotundus, a substitute for Aconitum heterophyllum: studies on the Ayurvedic concept of Abhava Pratinidhi Dravya (drug substitution). J Ayurveda Integr Med 2010;1(1):33–9.
[7] Anonymous. British Pharmacopoeia. London: General medical council pharmaceutical Press-1968: 17; 1209, 1227, 1267, 1268, 1276, 17–1276.
[8] Tarek N, Hassan HM, Ghani SMM, Radwan IA, Hammouda O, El-Gendy AO. Comparative chemical and antimicrobial study of nine essential oils obtained from medicinal plants growing in Egypt. J Basic Appl Sci 2014;3:14–156.
[9] Bhattacharjee AK, Das. Phytochemical screening of some indian plants. Quart J Crude Drugs Res 1969;9:1408–12.
[10] Sabu MC, Kuttan R. Antidiabetic and antioxidant activity of Terminalia belerica. Roxb Indian J Exp Biol 2009;47(4):270–5.
[11] Sabu CM, Kuttan R. Antidiabetic and antioxidant activity of *Terminalia belerica. Roxb*. Indian J Exp Biol 2009;47:270–5.
[12] Kumar A. Essentials perspectives for *Emblica officinalis*. IJPCS 2012;1(1).
[13] Krishnaveni M, Mirunalini S. Therapeutic potential of *Phyllanthus emblica* (amla): the ayurvedic wonder. J Basic Clin Physiol Pharmacol 2010;21(1):93–105.
[14] Abbas DA. Analgesic, anti-inflammatory and antidiarrhoeal effects of *Datura stramonium* hydroalcoholic leave extract in mice. IJRRAS 2013;14(1).
[15] Gupta S, Raghuvanshi M, Jain D. Comparative studies on anti-inflammatory activity of Coriandrum Sativum, Datura stramonium and *Azadirachta Indica*. Asian J Exp Biol Sci 2010;1(1):151–4.
[16] Girmay S. Preliminary Phytochemical screening and in vitro antimicrobial activity of *Datura stramonium* leaves extracts collected from Eastern Ethiopia. Int Res J Biol Sci 2015;4(1):55–9.
[17] Charpin D, Orehek J, Velardocchio JM. Bronchodilator effects of antiasthmatic cigarette smoke (*Datura stramonium*). Thorax 1979;34(2):259–61.
[18] Aparna, Joshi K, Abhishek J, Vyas M, et al. Phyto-chemical and pharmacological profiles of *hyoscyamus Niger* Linn. (*parasika yavani) a* review. Pharma Sci Monit 2015;6(1):153–8.
[19] Anonymous. The Wealth of India-A dictionary of Indian raw materials, vol. 1st and vol. 7. New Delhi: National Institute of Science Communication, Council of Scientific and Industrial Research; 2003.
[20] Dulger G, Dulger B. Antimicrobial activity of the seeds of *Hyoscyamus Niger* L. (Henbane) on microorganisms isolated from urinary tract infections. J Med Plants Stud 2015;3(5):92–5.
[21] Dorman HJD, Surai D, Deans SG. In vitro antioxidant activity of a number of plant essential oils and Phytoconstituents. J Essent Oil Res 2000;12:241–8.
[22] Lee KG, Shibamoto T. Antioxidant property of aroma extract isolated from clove buds *Syzygium aromaticum* (L.) Merr. Et Perry. Food Chem 2001;74(4):443–8.
[23] Khare CP. Indian Medicinal plant: an illustrated dictionary. New York: Springer Science + Business Media; 2007.
[24] Ghelardini C, Galeotti N, Di Cesare Mannelli L, Mazzanti G, Bartolini A. Local anaesthetic activity of β-caryophyllene. Farmaco 2001;56:387–9.
[25] Anonymous. Standardization of single drugs of Unani medicine, Part1st & 5th. New Delhi: CCRUM, Minisrty of Health and Family Welfare, Department of AYUSH; 2006.
[26] Anonymous. The Unani Pharmacopoeia of India. Vol.1,V. New Delhi. AYUSH Ministry of Health & Family Welfare. Govt. of India; 2007.
[27] Singh E. Phytochemistry, traditional uses and cancer chemopreventive activity of Amla *(Phyllanthus emblica)*: the Sustainer. J Appl Pharmaceut Sci 2011;02(01):176–83.
[28] Evans WC. Trease and evans. Pharmacognosy. New Delhi: Elsevier; 2008.
[29] Kokate CK. Pharmacognosy. Pune: Nirali Prakashan; 2012.
[30] Wadud A, Ahmad G, Sofi G, Iqbal SF. Temperament and action of Unani drugs: an integrated approach. Indian J Unani Med 2010;III(I):23–30.
[31] Khan MA. Muheete azam. New Delhi: CCRUM, ministry of health and family welfare, govt. of India, vol. 1st & 3rd; 2013.

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[32] He M, Tian H, Luo X, Qi X, Chen X. Molecular progress in research on fruit astringency. Molecules 2015;20:1434–51.
[33] Edewor-Kuponiyi TI. Plant-derived compounds with potential sedative and anxiolytic activities. Int J Basic Appl Sci 2013; July;02(01):63–78.
[34] Platel K, Srinivasan K. Digestive stimulant action of spices: a myth or reality? Indian J Med Res 2004;119:167–79.
[35] Ali B, Al-Wabel NA, Shams S, Ahamad A, Khan SH, Anwar F. Essential oils used in aromatherapy: a systemic review. Asian Pac J Trop Biomed 2015;5(8):601–11.
[36] Girach RD, Siddiqi PA, Singh SS. Phytochemistry in relation to temperament of plant drugs, proceding of national seminar on research methodology in Unani medicine. New Delhi: Jamia Hamdard; 1995. p. 152–5.

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