# Liver Admittance: Biomarker for drug toxicity and herbal healing

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Excessive use of antibiotics has side effects on the bio-system. The biochemical reasons for such effects are not always known. In this study, the impact of Amoxicillin, AM, on the liver tissue was investigated by a physical parameter, admittance spectroscopy. Also, the effect of a natural supplement, Ashwagandha seeds extract (ASE) (100, 200, 300 mg/kg) as a protective agent taken with AM and as a therapeutic agent given after ceasing AM were measured by comparing their effects on the liver admittance. Results showed a reduction in liver admittance, reaching its maximum reduction with the highest dose of protection groups, and a reverse of the electrical behavior of liver as a result of AM toxicity. On the other side, the protective and therapeutic ASE reduced AM–induced liver toxicity. By comparing the role of protective and therapeutic ASE, the therapeutic doses could restore the admittance values nearer to control. These findings proved that electrical admittance can be used as a sign of liver tissue status.

## Keywords
Admittance; Ashwagandha seed extract; Amoxicillin; Liver

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***Receive Date: 20 Aug. 2024; Revise Date: 3 Sep. 2024; Accept Date: 5 Sep.2024; Publish: 6 Sep. Month 2024***

## 1. Introduction

Wrire A lot of studies concern well-known drugs that are normally used but with intake profusely. These drugs cause acute or chronic liver injury. The scientists named this case “Drug-induced liver injury (DILI)”. These drugs include Amoxicillin- clavulanate, Flucloxacillin, trovafloxacin, Hydralazine, and Atorvastatin [1-4]. Some works revealed that the action mechanism of these drugs is that antigen-specific T cells, as well as cytokines, are increased tumor necrosis factor- α (TNF-α) and interferon- γ (IFN-γ). IFN-γ probably induces TNF-α formation, initiating cellular injuries and ending with cell death. They suggested that the action of IFN-γ and TNF-α is synergistic [5, 6].

Previous studies revealed that amoxicillin treatment with overdose can cause oxidative stress which leads to an imbalance in the bio-system and oxidation of cell membrane lipid, DNA and RNA molecules, and cellular proteins causing toxicity of different organs including the liver tissue [7, 8]. Biomarkers of hepatotoxicity include a rise of liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and also histopathological disorders such as necrosis of hepatocytes and phagocytic infiltration [9].

Therefore, in this work, we utilized one of the medicinal plants known for its ability to detoxify the foreign components inside the bio-system as it contains a lot of antioxidants; Ashwagandha or *Withania somnifera*. This plant contains more than 40 withanolides, lignan-amides, and steroidal saponins [10, 11]. These phytochemicals are responsible for the ability of Ashwagandha to modulate the immune function [12, 13], perform cardio protection from ischemia and reperfusion injury [14], and treat neurodegenerative diseases [15, 16]. Additionally, this plant has antibacterial [17, 18] and anti-inflammatory activities [19]. Moreover, the withanolides group derived from Ashwagandha can suppress the production of inflammatory cytokines and nuclear factor- Kabba B, NF-kB, induced by lipopolysaccharides [20, 21]. Accordingly, the authors thought that Ashwagandha can reverse the action mechanism of Amoxicillin which was revealed in the study of Roth et al. [6].

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Various studies exposed the ability of Ashwagandha roots and leaves to protect the liver from toxic compounds. Devkara et al. [**22**] exposed the hepatoprotective effect of withanolide-rich fraction (WRF) isolated from *Withania somnifera* root extract against acetaminophen (APAP) toxicity. Also, Aboobecker et al. [**23**] confirmed the hepatoprotective influence of ASH leaves against $CCl_4$ toxicity. Furthermore, the protective power of *Withaferin A* (*WA*), a natural compound derived from Ashwagandha, against bromobenzene-induced liver damage was shown by the study of Vedi and Sabina [**24**]. *WA* can stop the dysfunction of mitochondria by promoting the enzyme activities of mitochondria and balancing the Bcl-2 expression associated with X/Bcl-2 in the liver. Also, Abu Bakar et al. [**25**] displayed the hepatoprotective impact of *WA* with high-fat diet (HFD)-induced obese mice.

In this study, we have focused on Ashwagandha seeds extract hoping to detoxify the Amoxicillin-induced hepatotoxicity. Also, the physical parameter, electrical admittance, was used as a biomarker for discovering the AM-induced liver toxicity, where the sensitivity of dielectric parameters to discover the molecular, cellular and tissue changes was proved in previous works [26-36].

## 2. Experimental

### 2.1. Amoxicillin drug:

Bought Amoxicillin (AM) capsules were liquefied in distilled water to form a 90 mg/kg dose [**8**]. AM dose was administered orally to rats; 90 mg/kg/day for 12 days.

### 2.2. Plant material:

The source of Ashwagandha seeds was from Department of Horticultural Crops Technology in our institute.

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### 2.3. Preparation of extract:

Aqueous extract of Ashwagandha seeds was prepared by following the method mentioned in Maheswari and Manisha work [**37**].

### 2.4. Experimental animals:

Sprague-Dawley Male rats (110-120 g), were bought from the lab of Animal House in our institute, and kept in cages at a temperature of 23 ± 2 C. Animal management and all experimental steps followed the ethics of animal care and approval from Medical Ethical Committee of our institute with No. (05470723).

### 2.5. Experimental design:

Fifty-six rats were distributed into 8 groups (7 animals for each group):

1) **Control group** (G1): The animals were nourished with a basal diet for 12 days.
2) **Amoxicillin (AM) group** (G2): The animals received 90 mg/kg. b. wt., AM dose orally, daily for 12 days.
3) **Protective groups** (G3-5): Rats gavage orally AM dose, 90 mg/kg. b. wt., daily for 12 days. Along with, orally, ASE (100, 200, and 300 mg/kg), respectively, 2 hrs. after AM treatment.
4) **Therapeutic groups** (G6-8): Animals were given, orally, an AM dose, of 90 mg/kg. b. wt., daily for 12 days. 24 hrs. from ceasing AM, the groups (G6-8) were administered orally with ASE (100 mg/kg, 200 mg/kg, and 300 mg/kg) respectively, for 7 days.

### 2.6. Dielectric measurements:

#### 2.6.1. Liver sample preparation:

Liver samples of animals were obtained after abdominal incision and fixed in 10% formaldehyde solution. Liver slices were soaked in distilled water for one day., and

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then samples were placed in ethyl alcohol for 30 min in each concentration (50%, 70%, 90%, 95%, and 100%) respectively to dehydrate the samples [38].

### 2.6.2. Dielectric measurements:

Broadband Dielectric Spectrometer, Concept 40, from Novo Control, Germany was used to do Dielectric measurements. Two brass electrodes with a diameter of 10 mm, for the smaller one, were used for the measurements. The applied voltage was adjusted to $1V_{rms}$, with frequency from 0.1 Hz to 20 MHz, and temperature (10- 40 C) [38].

**Complex admittance, $Y^*$:**

The dielectric calculations have been carried out for all groups by the next formula:

Admittance '$Y$' can be measured as $Y^* = 1/Z^*$ (1)

'$Z^*$' is the complex impedance, $Z^* = R + iX$ (2)

Where '$i$' equals √-1. '$R$' is the resistance and '$X$' is the reactance, both form the real and imaginary parts of the impedance respectively **[39].**

## 3. Results

### 3.1. Liver Admittance:

#### 3.1.1. Real part of liver Admittance for Amoxicillin groups:

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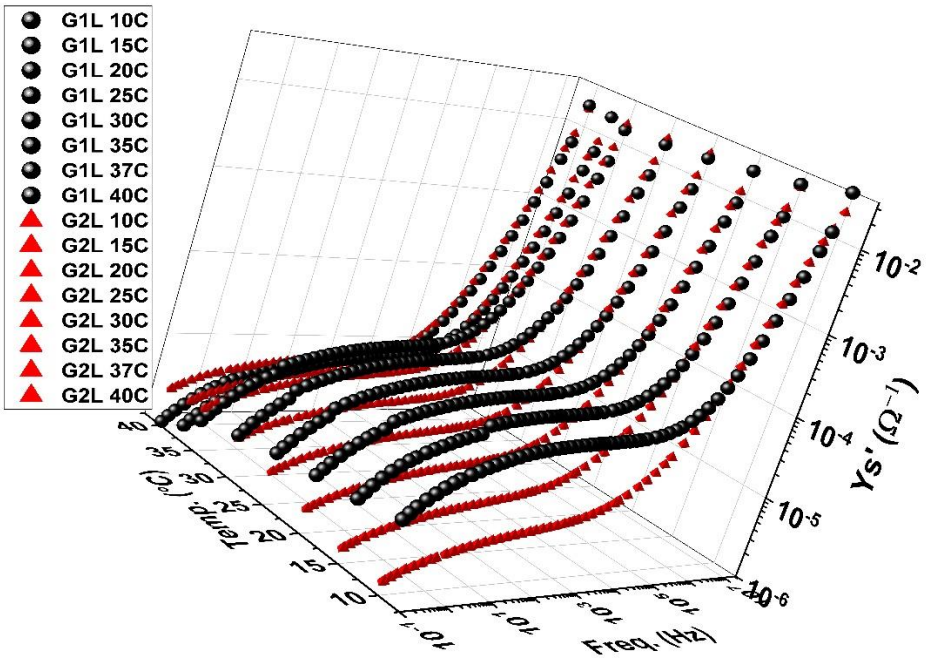


**Fig. 1.** Real part of liver Admittance in response to AM, G2, compared to control, G1. With temp. (10-40) C and freq. (0.1 Hz- 20 MHz). L: Liver

Fig. 1 shows the real part of electrical liver admittance in 3D with temperature (10-40) C and frequency (0.1Hz-20MHz) for control (G1L), and AM group treated with amoxicillin (G2L), 90mg/kg. As shown, admittance, Y', of liver reduced to about one-fifth for control due to AM interaction with tissue, except for temperature 40 C and ion channels in the membrane at physiological temperatures. Decreased Y' means that new difficulties and obstacles to current passage through liver tissue were not present before AM administration. Charge transfer behavior concerning temperature was reversed as a result of AM interactions within liver cells and tissue. This tells us there are other interactions of AM with liver tissue that are not known and should be investigated.

These changes point to hepatotoxicity which has other symptoms in the previous studies including increased levels of lipid peroxidation and liver enzymes, as well as cellular necrosis and cirrhosis [40-42].

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### 3.1.2. Real part of liver Admittance for protective ASE groups:

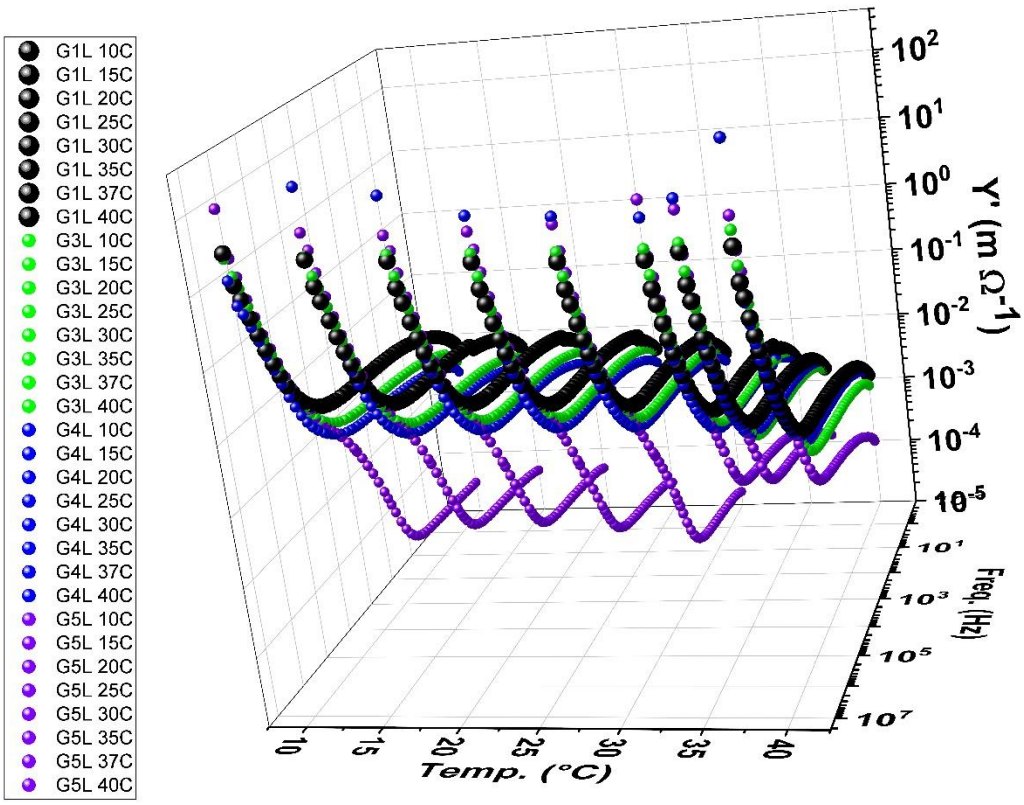


**Fig. 2.** Real part of liver admittance in response to protective ASE (G3-G5) compared to control, G1. With temp. (10-40) C and freq. (0.1 Hz- 20 MHz).

Fig. 2 explores 3D diagram (admittance- freq.-temp.) of real part of liver admittance responding to protective ASE doses compared to control. Using ASE as a protective natural supplement with AM dose did not completely restore the original Y' level Fig. 2. However, the lower dose (G3) achieved the nearest values to control, followed by the intermediate one. While increasing the concentration of the protective supplement to 300

mg/kg lowered Y' values even more. Such data refers to nonlinearity between the supplement dose and Y' level; suggesting an interaction of the ASE with liver tissues and/ or with AM.

### 3.1.3. Real part of liver Admittance for therapeutic ASE groups:

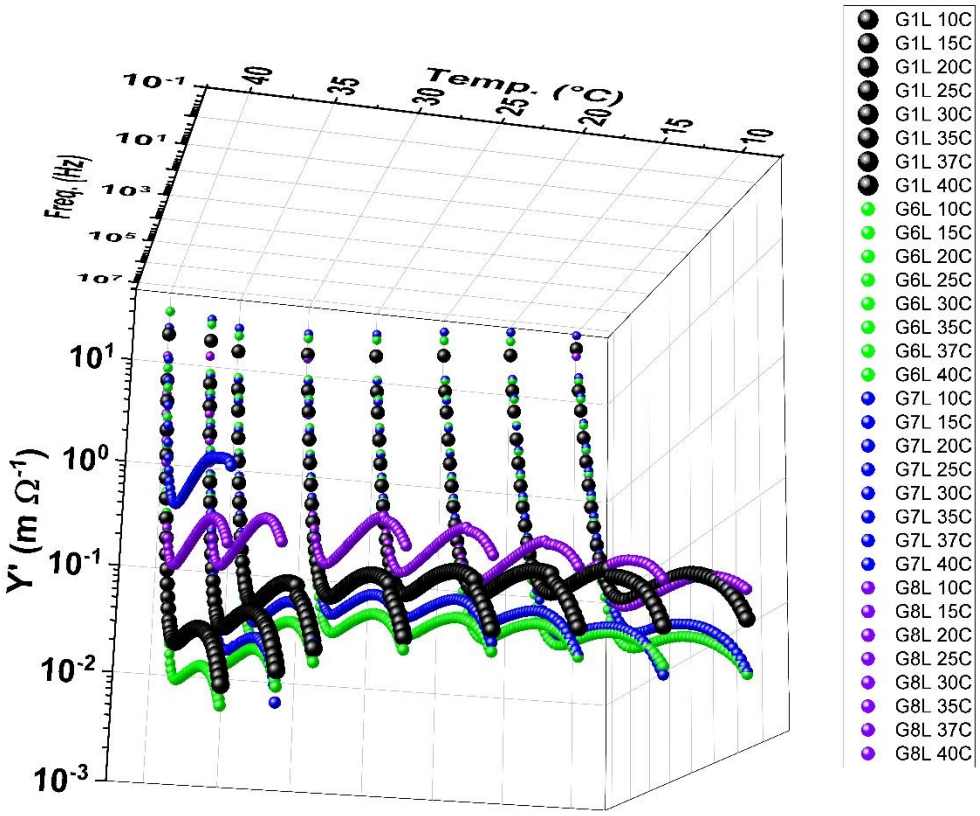


**Fig. 3.** Real part of liver Admittance in response to therapeutic ASE (G6-8) compared to control, G1. With temp. (10-40) C and freq. (0.1 Hz- 20 MHz).

Fig. 3 displays the 3D diagram of real part of liver admittance responding to therapeutic ASE (G6-8) compared to G1, With temp. (10-40) C and freq. (0.1 Hz- 20 MHz). Data of Fig. 3 showed that ceasing AM and giving ASE as a therapeutic agent led to different outcomes; the improvement of Y' values became dose-dependent, where the highest ASE

dose improved Y' values higher than that of control except at 40C where the intermediate dose got the highest Y' values.

Therefore, the data of therapeutic and protective ASE showed that ASE contents interact with AM itself. That is why the protective ASE did not enhance Y's level. Moreover, the results of therapeutic effect of ASE confirmed that Ashwagandha can adverse the action mechanism of Amoxicillin [**6**], where withanolides presented in Ashwagandha content can suppress the production of nuclear factor- Kabba B, inflammatory cytokines and NF-kB, induced by lipopolysaccharide [20,21].

### 3.1.4. Imaginary part of liver admittance for control &amoxicillin groups:

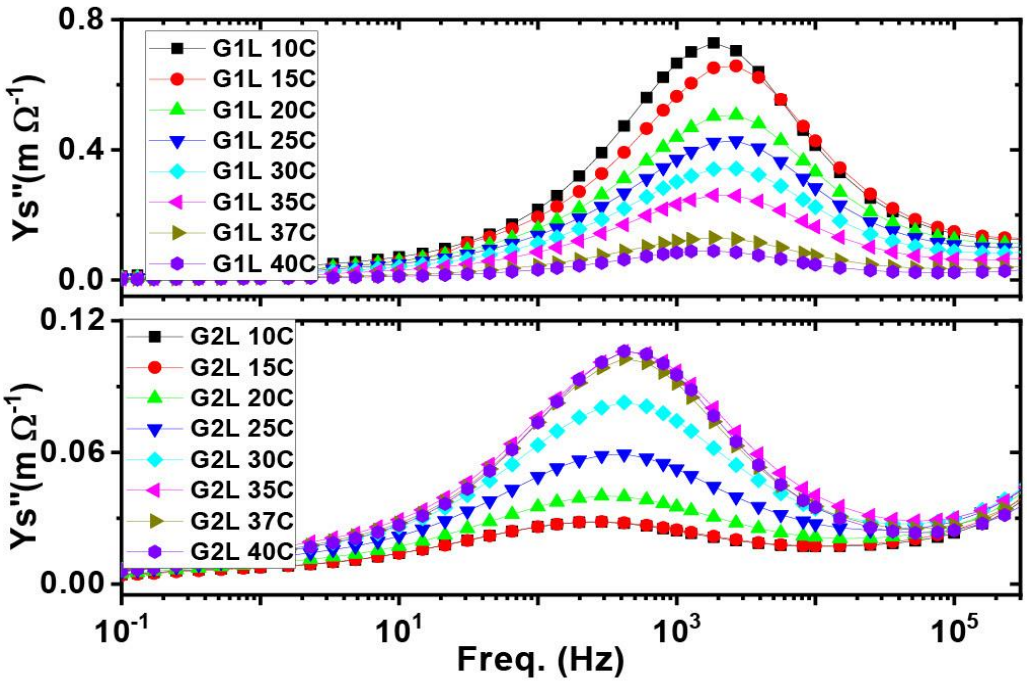


**Fig. 4.** Relaxation of liver admittance, Y", of G1L and G2L at temp. (10-40) C and frequency (0.1 Hz- 20 MHz).

Fig. 4 shows the imaginary part of liver admittance for control in upper graph and AM group in lower one with frequency (0.1Hz-20MHz) at temp. (10-40C). From Fig. 4, it can be seen that the relaxation of Y" of G2, AM treated group, is lagging behind the G1 group, where the peak of

admittance relaxation of G1 group is situated at about 2 kHz and that of the AM-treated group is located around 400 Hz. So, data represents the lag and difficulty of charge transfer imposed by AM interactions within liver cells and tissue. Another point is that AM administration caused the reversal of liver tissues' electrical response to temperature as shown in Fig. 4- G2L, the lower part of the figure.

### 3.1.5. Imaginary part of liver admittance for control & protected ASE groups:

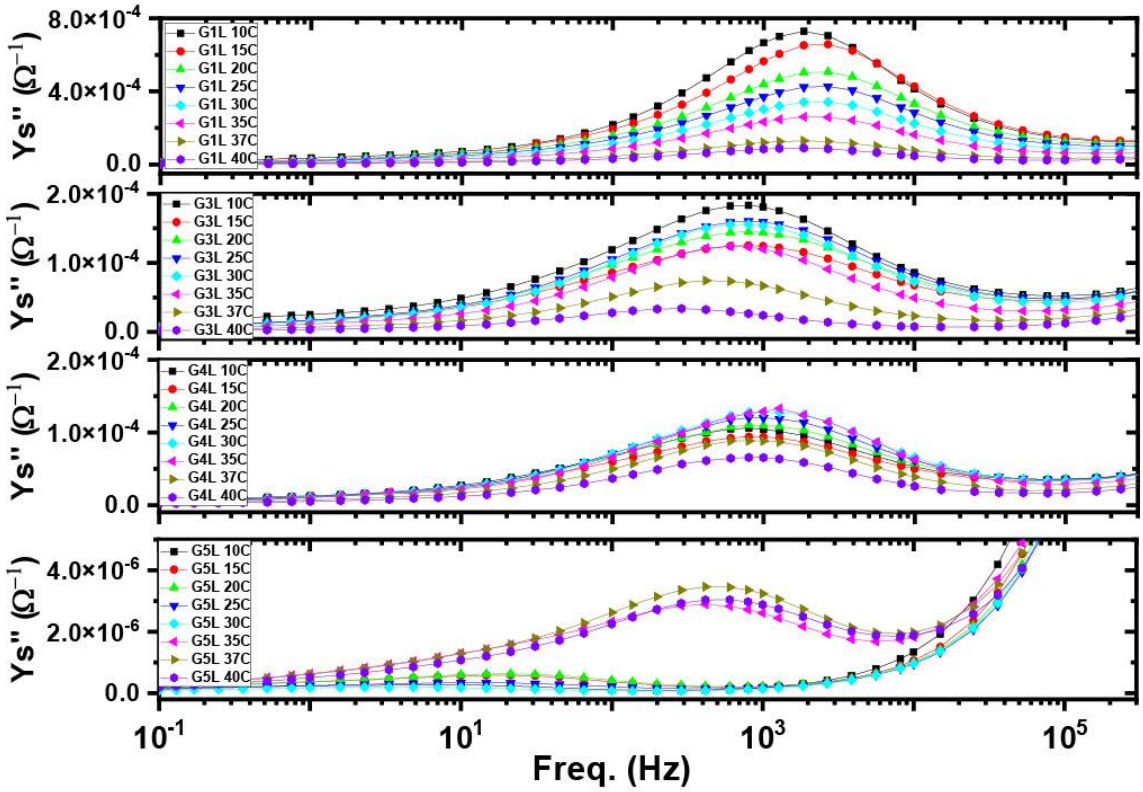


**Fig. 5.** Imaginary part of liver admittance, Y", of protective ASE (G3-G5) at temp. (10-40) C with frequency (0.1 Hz- 20 MHz) compared to control (G1L).

Fig. 5 represents the imaginary part of liver admittance for G1and protected groups of ASE (G3-5) with frequency (0.1Hz-20MHz) at temp. (10-40C). As shown in Fig. 5, ASE administration with AM (protective case) led to some sort of partial restoration of relaxation peak which

happened with G3, relaxation peak was at about 0.8 kHz and was even better with G4 having a relaxation peak of about 1 kHz. G5, the largest ASE dose, had a very bad effect on the relaxation peak which was about 10 to 20 Hz at low temperatures with distorted shape. At physiological temperatures, relaxation peak was about 40 Hz for G5. It can be seen that low ASE protective dose could restore the liver tissue to temperature response as control. The intermediate protective dose exhibited an intermediate phase toward the reversal of liver-temperature response to Y". The highest ASE protective dose caused a liver–temperature reversal of the Y" behavior.

### 3.1.6. Imaginary part of liver admittance for control & therapeutic ASE groups:

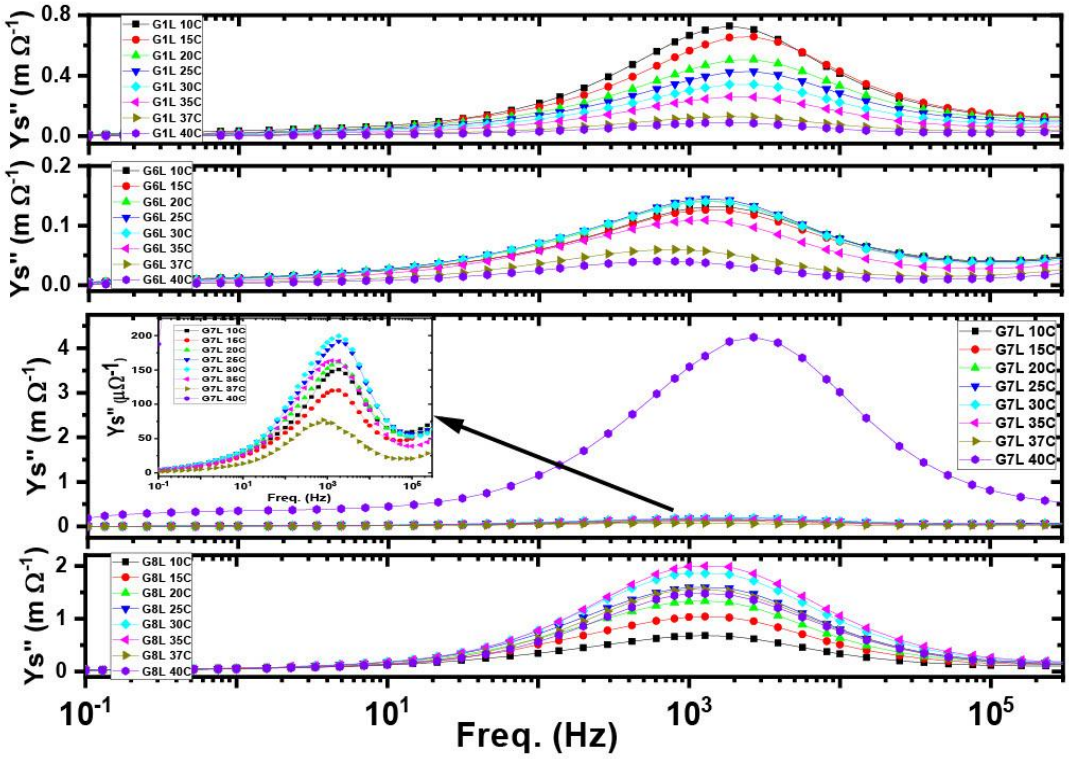


**Fig. 6.** Imaginary part of liver admittance, Y", of therapeutic ASE (G6-G8) at temp. (10-40) C with frequency (0.1 Hz- 20 MHz) compared to control (G1L).

Fig. 6 displays the imaginary part of liver admittance, Y", of therapeutic ASE (G6-G8) at temp. (10-40) C with frequency (0.1 Hz- 20

MHz) compared to G1L. As seen in this figure, stopping AM administration and starting to supply rats with ASE (therapeutic case) had better results than the protective groups. Where the smallest amount of ASE, G6, had restored the relaxation time values nearest to the control level. The intermediate ASE dose had almost the same relaxation time as that of the control. The highest dose of ASE decreased the relaxation time slightly. One common feature that was proportional to the ASE dose is the behavioral disturbance of **Y"**'s relaxation peak with temperature starting at G6 increasing through G7 and reaching almost a complete inversion of the relaxation behavior with temperature at G8. As we can see lower temperature has the lowest peak at G8. This indicates that ASE affects the liver tissue. The peak height of Y" is decreased to one eighth by the lowest ASE therapeutic dose. Raised to one fourth (200 $\mu\ \Omega^{-1}$) of the control by the intermediate ASE therapeutic dose, except at 40C where the admittance peak reached 4 m $\Omega^{-1}$. The highest therapeutic dose had almost complete reversal of the liver- temperature behavior for Y" and achieving a 2 m $\Omega^{-1}$ peak height, i.e. about three times the peak height of control.

**Conclusion:**

A sensitive dielectric parameter investigated the side effects of Amoxicillin on liver tissue; admittance. Also, Ashwagandha seeds extract (ASE) was used as a protective and therapeutic supplement in doses of 100, 200, and 300mg/kg, for both cases to weaken or eliminate the AM interaction. Data showed that AM interaction with the liver led to a reduction in liver admittance and a reversal of the electrical behavior of liver tissue. This indicated the difficulties faced by current passage through the liver. By comparing the protective and therapeutic ASE results, the therapeutic case had better results as their doses restored the relaxation time values near the control level. This pointed to the probability of ASE -AM interaction, so when AM was ceased, the results of liver admittance improved. Moreover, this work pointed out that ASE also reverses the electrical behavior of the liver tissue with respect to temperature.

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**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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