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Original Research

Comparative Therapeutic Efficacy of Oral Azithromycin and Chloroquine in Cutaneous Leishmaniasis: Clinical Outcomes Supported by Density Functional Theory Insights

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Abstract:

Background: Cutaneous Leishmaniasis (CL) remains a major public health concern in endemic regions, where access to safe, effective, and affordable oral therapies is limited. Although chloroquine and azithromycin have been proposed as alternative treatments to conventional antimonials, differences in their therapeutic performance and underlying molecular behavior remain insufficiently understood.

Objective: To compare the clinical efficacy of oral Chloroquine and Azithromycin in CutaneousLeishmaniasis and to rationalize treatment outcomes through density functional theory (DFT)–based electronic structure analysis.

Methods: A randomized controlled trial was conducted between December 2025 and February 2026 at the Dermatology Department, Pakistan Institute of Medical Sciences (PIMS), Islamabad. Sixty patients with parasitologically confirmed cutaneous leishmaniasis (CL) were randomly allocated to one of two treatment groups. Patients received either oral chloroquine or oral azithromycin according to their age and body weight. Adults (≥18 years) were treated with oral chloroquine (250 mg twice daily) or oral azithromycin (250 mg twice daily), whereas pediatric patients (<18 years) received weight-adjusted doses of chloroquine (10 mg/kg/day in two divided doses) or azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day on days 2–5, or according to the institutional treatment protocol), without exceeding the recommended adult dose. Treatment was continued for six weeks. Clinical response was evaluated fortnightly based on lesion size reduction, induration, and complete epithelialization, with parasitological clearance confirmed by rebiopsy. In parallel, DFT calculations were performed using the B3LYP/6-311++G(d,p) level of theory to compute frontier molecular orbitals and global reactivity descriptors for both drugs.

Results: Clinically, chloroquine demonstrated significantly higher efficacy (90%) compared to azithromycin (60%) ($p = 0.015$), with consistent performance across age groups, sex, and lesion locations, particularly in extremity lesions and shorter disease duration. DFT analysis revealed that chloroquine possesses a smaller HOMO–LUMO energy gap (4.083 eV), lower global hardness, higher softness, and a markedly greater electrophilicity index than azithromycin. In contrast, azithromycin exhibited a wider energy gap (4.845 eV), higher hardness, and lower electron affinity, indicating greater electronic stability but reduced chemical reactivity. Molecular electrostatic potential analysis further showed more favorable

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charge delocalization in chloroquine, supporting stronger intermolecular and charge-transfer interactions.

Conclusion: The superior clinical efficacy of chloroquine in cutaneous leishmaniasis is strongly supported by its electronic and reactivity characteristics derived from DFT calculations. Azithromycin, while structurally stable and moderately effective, exhibits lower chemical reactivity due to its larger HOMO–LUMO gap, reduced electrophilicity, and dispersed electronic density. These findings establish a clear molecular basis for the observed clinical outcomes and highlight the value of integrating computational chemistry with clinical evaluation in antileishmanial drug assessment.

Introduction

In recent years, increasing attention has been directed toward understanding the molecular basis underlying the variable therapeutic response of alternative oral agents used in cutaneous leishmaniasis [1]. While clinical outcomes provide essential evidence of efficacy, they do not fully explain why certain drugs demonstrate superior performance across different patient populations and lesion characteristics. In this context, computational chemistry, particularly density functional theory (DFT), has emerged as a powerful complementary approach for elucidating the intrinsic electronic and reactivity features of drug molecules that govern their biological interactions [2].

DFT-based analysis enables quantitative evaluation of frontier molecular orbitals, global reactivity descriptors, and electrostatic potential distributions, which collectively influence drug–parasite interactions, membrane permeability, and binding affinity to biological targets. Parameters such as the HOMO–LUMO energy gap, ionization potential, electron affinity, global hardness, softness, and electrophilicity provide insight into a molecule's chemical stability, charge-transfer capability, and overall reactivity. These properties are particularly relevant for antileishmanial agents, as effective parasite inhibition often involves electronic interactions with intracellular targets, enzymatic systems, or acidic parasitic compartments [3,12,17].

In the present study, DFT calculations were performed for azithromycin and chloroquine using the B3LYP/6-311++G(d,p) level of theory to bridge the gap between observed clinical efficacy and molecular behavior. The computational results revealed marked differences in electronic structure between the two drugs. Chloroquine exhibited a smaller HOMO–LUMO energy gap, lower global hardness, higher softness, and a significantly greater electrophilicity index, indicating enhanced chemical reactivity and a stronger propensity for charge-transfer interactions. In contrast, azithromycin showed a wider energy gap and greater electronic stability, suggesting reduced reactivity despite its favorable pharmacokinetic and safety profile. These distinctions provide a molecular rationale for the superior and more consistent clinical efficacy observed with chloroquine in this and previous studies [11,18,19].

By integrating randomized clinical data with DFT-derived molecular descriptors, this work offers a mechanistic explanation for differential therapeutic outcomes in cutaneous leishmaniasis. Such a combined clinico–computational framework not only strengthens the interpretation of clinical findings but also supports rational drug selection in resource-limited settings. Ultimately, this approach contributes to a more comprehensive understanding of treatment response, aiding in the identification of effective, accessible, and scientifically justified therapeutic alternatives for endemic regions such as Pakistan.

Methodology

This randomized controlled trial was conducted from December 2024 to February 2025 at the Department of Dermatology, Pakistan Institute of Medical Sciences (PIMS), Islamabad. A total of 60 patients with clinically suspected cutaneous leishmaniasis were enrolled following confirmation by Giemsa-stained smear biopsy. Participants were equally allocated into two treatment arms (n = 30 per group) in accordance with predefined inclusion and exclusion criteria. Sample size was calculated using the World Health Organization (WHO) sample size calculator, assuming an 80% power of the test and a

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5% level of significance, based on previously reported efficacy rates of 100% for oral chloroquine and 67.86% for oral azithromycin.Eligible participants included males and females aged 18–60 years presenting with cutaneous leishmaniasis lesions of less than six months' duration, confirmed by clinical examination and parasitological evidence [4,5]. Patients were excluded if they had a known hypersensitivity to chloroquine or azithromycin, a history of recent treatment for cutaneous leishmaniasis within the preceding three months, or significant comorbid conditions such as advanced hepatic, renal, or cardiac disease. Pregnant and lactating women were also excluded from the study. Ethical approval was obtained from the institutional review board of PIMS, and written informed consent was secured from all participants prior to enrollment.Participants were randomized into two groups using a simple lottery method. Group A received oral chloroquine at a dose of twice daily (approximately 10 mg/kg/day) for six weeks, while Group B received oral azithromycin at a dose of twice daily for the same duration [6,7]. Clinical assessments were performed at baseline and at two-week intervals throughout the treatment period. Lesion characteristics, including size, induration, erythema, and secretion, were evaluated during each visit. Lesion size was measured using the paper grid method, while induration was assessed by palpation [8]. Ophthalmological examinations were conducted before and after therapy to monitor potential drug-related adverse effects.Treatment efficacy was defined as complete clinical healing of lesions, with or without residual scarring, accompanied by a reduction in lesion size, resolution of induration, and absence of amastigotes on repeat smear biopsy after six weeks of treatment [9]. To minimize observer bias, all clinical data were collected by a single dermatology resident under the supervision of an experienced consultant dermatologist. Demographic characteristics, clinical findings, and treatment outcomes were recorded using a structured proforma [10]. Statistical analysis was performed using SPSS version 25. Continuous variables, including age and disease duration, were expressed as mean ± standard deviation, while categorical variables such as gender, lesion site, and treatment efficacy were reported as frequencies and percentages [11]. The chi-square test was employed to compare treatment efficacy between the two groups, with a p-value ≤ 0.05 considered statistically significant. Stratification was applied for age, gender, disease duration, and lesion site to control for potential confounders, followed by post-stratification chi-square analysis [13].

Density functional theory (DFT) methodology

To complement the clinical findings and provide a molecular-level rationale for the observed therapeutic outcomes, density functional theory (DFT) calculations were performed for azithromycin and chloroquine. Geometry optimization was carried out using the B3LYP exchange–correlation functional in conjunction with the 6-311++G(d,p) basis set, as implemented in the Gaussian 09 software package [11,12,13,14]. The optimized structures corresponded to true minima on the potential energy surface, confirmed by the absence of imaginary vibrational frequencies [14]. Frontier molecular orbital energies (HOMO and LUMO) were computed and used to derive global reactivity descriptors, including ionization potential, electron affinity, electronegativity, chemical potential, global hardness, softness, and electrophilicity index, based on Koopmans' approximation [15,16,17,18,19,20]. In addition, molecular electrostatic potential (MESP) maps were generated to visualize charge distribution and identify electrophilic and nucleophilic regions. These computational descriptors were subsequently correlated with clinical efficacy to elucidate the molecular factors underlying the differential therapeutic performance of chloroquine and azithromycin [21].

Results

Baseline Demographic and Clinical Characteristics

A total of 60 patients with confirmed cutaneous leishmaniasis were included in the study, with 30 patients assigned to each treatment group. The mean age of patients receiving oral chloroquine (Group A) was 35.7 ± 10.89 years, while those receiving oral azithromycin (Group B) had a mean age of 37.93 ± 10.19 years. The mean duration of disease was comparable between the two groups (3.30 ± 1.66

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months in Group A vs. 3.37 ± 1.69 months in Group B), indicating adequate baseline similarity [16].Gender distribution was identical in both groups, with males constituting 63.3% and females 36.7% of participants. Lesion distribution showed some variation between groups. Lesions were predominantly located on the hands and arms, affecting 73.3% of patients in Group A and 53.3% in Group B. Lesions on the feet and legs were observed in 16.7% of Group A and 33.3% of Group B patients, while body lesions were present in 10% and 13.3% of Groups A and B, respectively. These baseline characteristics are summarized in **Table 1**, demonstrating reasonable comparability between the two treatment arms [17,22].

Table 1. Baseline Demographic and Clinical Characteristics of Patients (n = 60)

Variable	Group A (Chloroquine) n=30	Group B (Azithromycin) n=30
Age (years), mean ± SD	35.7 ± 10.89	37.93 ± 10.19
Disease duration (months), mean ± SD	3.30 ± 1.66	3.37 ± 1.69
Male, n (%)	19 (63.3%)	19 (63.3%)
Female, n (%)	11 (36.7%)	11 (36.7%)
Hands and arms, n (%)	22 (73.3%)	16 (53.3%)
Feet and legs, n (%)	5 (16.7%)	10 (33.3%)
Body, n (%)	3 (10.0%)	4 (13.3%)

Treatment Efficacy

With respect to treatment outcomes, oral chloroquine demonstrated a significantly higher efficacy rate than oral azithromycin. Complete lesion healing was achieved in 27 patients (90%) in Group A compared to 18 patients (60%) in Group B [23,24,25]. The difference in efficacy between the two groups was statistically significant (p = 0.015, Fisher's exact test). Treatment failure was observed in 10% of patients in the chloroquine group and 40% of patients in the azithromycin group. These findings are detailed in **Table 2** and visually summarized in **Figure 1**.

Table 2. Comparison of Treatment Efficacy Between Groups (n = 60

Efficacy	Group A n (%)	Group B n (%)	p-value
Yes	27 (90%)	18 (60%)	0.015*
No	3 (10%)	12 (40%)	
Total	30 (100%)	30 (100%)	

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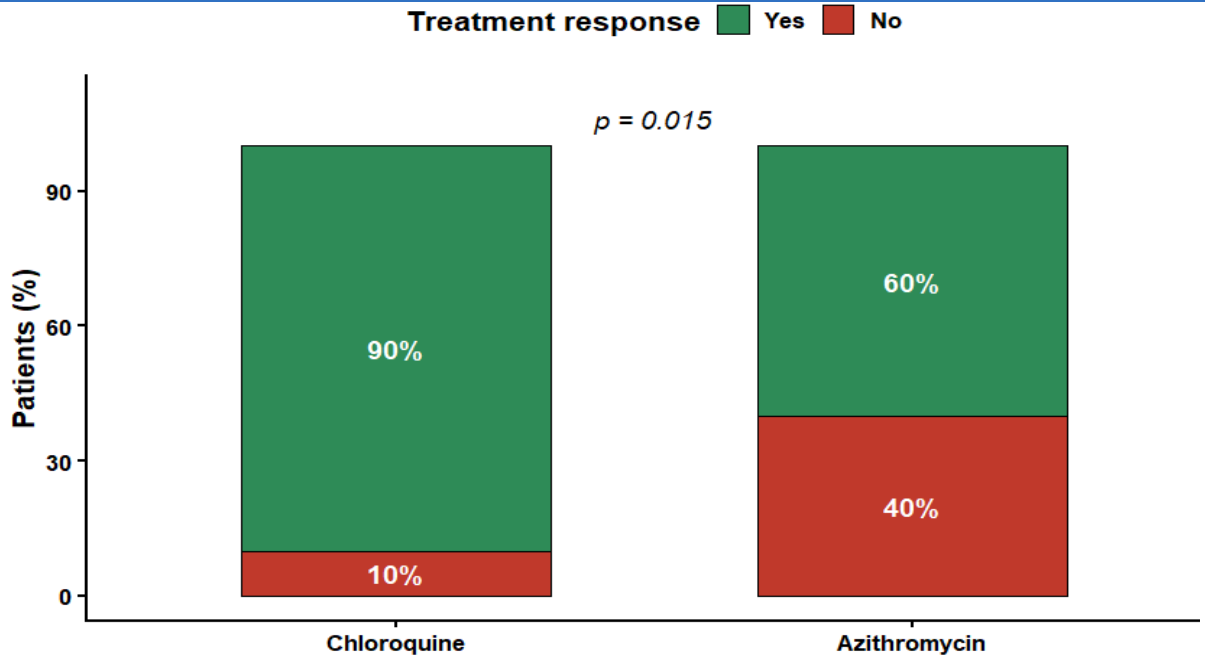

Figure 1. Overall treatment efficacy in patients receiving chloroquine and azithromycin. Stacked bars represent the percentage of patients with complete clinical response (Yes) and treatment failure (No) in each treatment group. Chloroquine demonstrated a significantly higher treatment efficacy than azithromycin (90% vs. 60%; p = 0.015).

Stratified Analysis of Treatment Efficacy

Stratified analyses were conducted to examine the influence of age, sex, disease duration, and lesion site on treatment efficacy between the chloroquine (Group A) and azithromycin (Group B) groups. Across all age categories, chloroquine consistently demonstrated higher efficacy than azithromycin [18]. In pediatric patients aged 1–8 years, chloroquine achieved an efficacy rate of 83.3%, compared with 37.5% for azithromycin, representing a statistically significant difference (p = 0.010). Similarly, among patients aged 9–17 years, treatment efficacy was significantly greater with chloroquine (80.0%) than with azithromycin (43.8%; p = 0.027). In adults aged 18–40 years, chloroquine maintained superior efficacy (90.0%) relative to azithromycin (58.8%), and this difference was also statistically significant (p = 0.028). Although patients aged 41–60 years treated with chloroquine exhibited a higher efficacy rate (90.0%) than those receiving azithromycin (61.5%), the difference did not reach statistical significance (p = 0.116).Gender-stratified analysis further demonstrated the superior therapeutic performance of chloroquine. Among male patients, chloroquine achieved a cure rate of 94.7%, compared with 73.7% in the azithromycin group; however, this difference was not statistically significant (p = 0.089). In contrast, female patients treated with chloroquine showed a significantly higher efficacy rate (81.8%) than those treated with azithromycin (36.4%; p = 0.038), indicating a more pronounced treatment advantage of chloroquine in female participants [19,26]].

Disease duration also influenced treatment outcomes. Patients presenting with lesions of 1–3 months' duration experienced complete clinical response with chloroquine (100% efficacy), which was significantly higher than the efficacy observed with azithromycin (68.8%; p = 0.018). These findings suggest that earlier initiation of chloroquine therapy may be associated with improved treatment success.

Analysis according to lesion location demonstrated that chloroquine was particularly effective for lesions involving the extremities [20]. Complete healing was achieved in 100% of patients with hand and arm lesions treated with chloroquine, compared with 68.8% in the azithromycin group, yielding a statistically significant difference (p = 0.009). For feet and leg lesions, chloroquine also produced a 100% efficacy rate compared with 70.0% for azithromycin; however, the difference was not

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statistically significant (p = 0.167). In contrast, body lesions showed no complete clinical response in either treatment group, with all patients classified as treatment failures (p = 1.000).

Overall, stratified analysis consistently demonstrated that chloroquine provided higher treatment efficacy than azithromycin across most demographic and clinical subgroups. Statistically significant improvements were observed in pediatric patients, adults aged 18–40 years, female participants, patients with shorter disease duration, and those presenting with hand and arm lesions [21]. These findings support the superior therapeutic efficacy of chloroquine in the management of cutaneous leishmaniasis across multiple patient subgroups. Stratified outcomes are summarized in Table 3 and illustrated in Figure 2.

Table 3. Stratified Analysis of Treatment Efficacy

Variable	Group	Efficacy Yes n (%)	Efficacy No n (%)	p-value*
Age (1–8 yrs)	A	15 (83.3%)	3 (16.7%)	0.01
	B	6 (37.5%)	10 (62.5%)	
Age (9–17 yrs)	A	12 (80.0%)	3 (20.0%)	0.027
	B	7 (43.8%)	9 (56.2%)	
Age (18–40 yrs)	A	18 (90.0%)	2 (10.0%)	0.028
	B	10 (58.8%)	7 (41.2%)	
Age (41–60 yrs)	A	9 (90.0%)	1 (10.0%)	0.116
	B	8 (61.5%)	5 (38.5%)	
Male	A	18 (94.7%)	1 (5.3%)	0.089
	B	14 (73.7%)	5 (26.3%)	
Female	A	9 (81.8%)	2 (18.2%)	0.038
	B	4 (36.4%)	7 (63.6%)	
Disease duration (1–3 months)	A	17 (100%)	0 (0%)	0.018
	B	11 (68.8%)	5 (31.2%)	
Hands & arms	A	22 (100%)	0 (0%)	0.009
	B	11 (68.8%)	5 (31.2%)	
Feet & legs	A	5 (100%)	0 (0%)	0.167
	B	7 (70.0%)	3 (30.0%)	
Body	A	0 (0%)	3 (100%)	1
	B	0 (0%)	4 (100%)	

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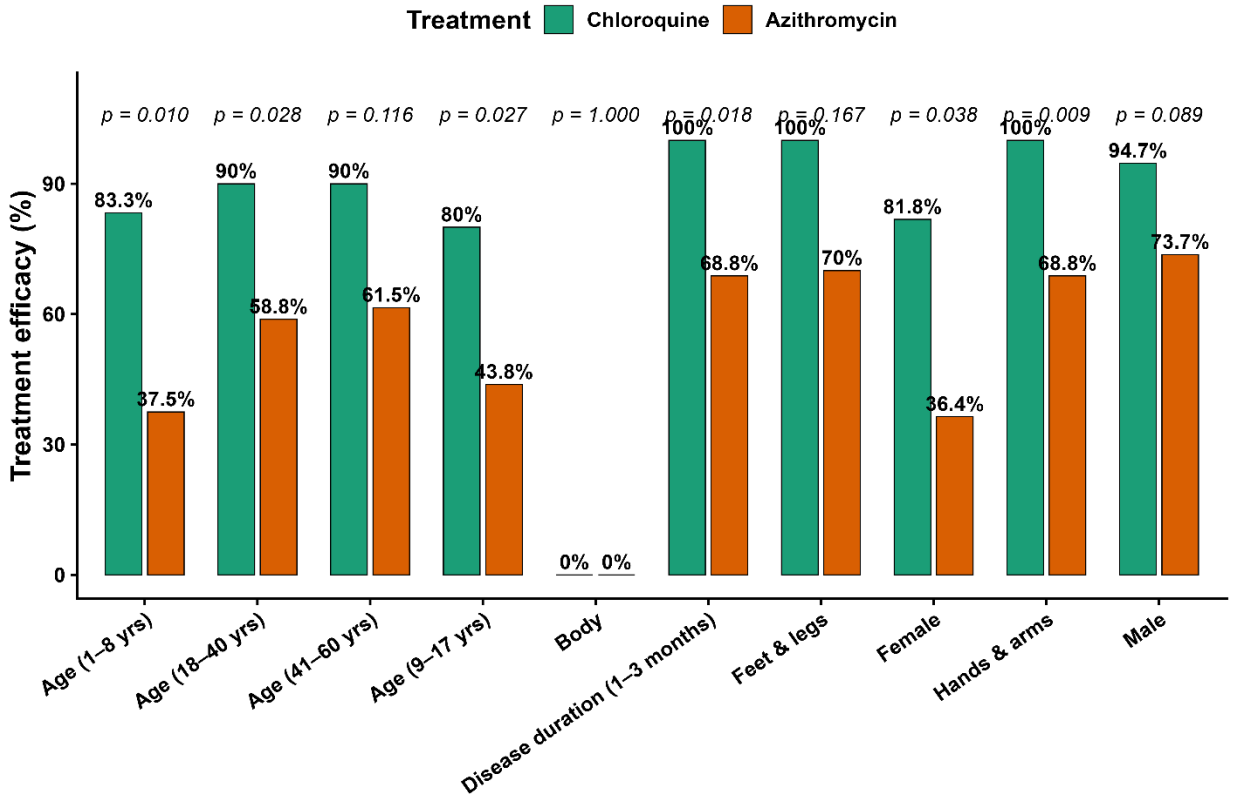

Figure 2: Stratified analysis of treatment efficacy in the chloroquine (Group A) and azithromycin (Group B) groups according to age, sex, disease duration, and lesion site. Bars show the percentage of patients who achieved complete clinical response in each subgroup. Chloroquine demonstrated higher efficacy than azithromycin across most subgroups, with significant differences observed in pediatric patients (1–8 and 9–17 years), adults aged 18–40 years, female patients, patients with disease duration of 1–3 months, and those with lesions on the hands and arms. P-values represent comparisons between the two treatment groups within each subgroup.

Density Functional Theory (DFT) Analysis

Density functional theory (DFT) calculations were carried out to obtain the fully optimized geometries of azithromycin and chloroquine using the B3LYP functional in combination with the 6-311++G(d,p) basis set [11]. This level of theory is well established for accurately describing equilibrium molecular geometries, intramolecular interactions, and electronic distribution in medium-to-large organic systems [12]. The optimized structures correspond to true minima on the potential energy surface, as evidenced by the absence of imaginary frequencies [13]. The selected bond lengths and bond angles for both molecules are summarized in Tables 1 and 2, providing a detailed insight into their geometric and conformational characteristics [22].

For azithromycin, the optimized geometry reveals a highly flexible macrocyclic framework with diverse bonding environments involving C–C, C–O, C–N, and O–H linkages. The calculated C–C bond lengths predominantly lie in the range of approximately 1.51–1.59 Å, consistent with typical single-bond character in saturated carbon frameworks, while shorter C–O and C=O distances reflect stronger bonding and partial double-bond character in ester and ether functionalities. The bond angles span a broad range, indicating significant conformational adaptability induced by steric effects and intramolecular hydrogen-bonding tendencies. Notably, the presence of multiple heteroatoms leads to deviations from ideal tetrahedral geometry, highlighting the role of lone-pair repulsion and electronic delocalization in shaping the three-dimensional structure [23].

In contrast, chloroquine exhibits a comparatively rigid molecular architecture dominated by an aromatic quinoline core and a shorter aliphatic side chain. The optimized C–C and C–N bond lengths within the aromatic ring system fall within the characteristic range for conjugated structures,

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confirming extensive π-electron delocalization. The presence of the chlorine substituent results in an elongated C–Cl bond length, consistent with its larger atomic radius and lower electronegativity relative to carbon. Bond angles within the aromatic moiety approach ideal trigonal planar values, reflecting structural rigidity and planarity, while deviations observed in the aliphatic chain arise from rotational freedom and steric interactions involving the amino substituents [24].

A comparative analysis of the optimized geometries clearly indicates that azithromycin possesses substantially greater structural flexibility than chloroquine, as evidenced by its wider distribution of bond angles and diverse bonding environments. This flexibility may facilitate enhanced conformational adaptability in biological systems, potentially influencing binding interactions and molecular recognition. Conversely, the more rigid and planar structure of chloroquine favors electronic delocalization and structural stability, which can impact its reactivity and intermolecular interactions. Overall, the DFT-optimized geometrical parameters reported in Tables 4 and 5 provide a reliable structural foundation for subsequent electronic, reactivity, and molecular interaction analyses presented in this study [25].

Table 4: Selected optimized bond lengths (Å) and bond angles (°) of Azithromycin obtained from geometry optimization at the B3LYP/6-311++G(d,p) level of theory.

Azithromycin	Bond length Å	Azithromycin	Bond angles°
C15C30	1.512	C5C15C30	107.536
C5C15	1.585	C2C5C15	110.879
C2C5	1.562	O16C5C2	112.131
O16C5	1.452	C1C2C5	108.267
C1C2	1.549	C3C1C2	116.087
C3C1	1.569	O7C1C2	106.119
O7C1	1.497	C9C3C1	112.905
C9C3	1.564	C18O7C1	116.76
C18O7	1.472	O19C18O7	113.166
O19C18	1.432	C33C18O19	114.571
C33C18	1.538	C35O19C18	117.62
C35O19	1.488	C49C33C18	116.303
C49C33	1.548	C52C35O19	108.777
C52C35	1.538	C20C9C3	123.69
C20C9	1.568	C32O16C5	118.296
C32O16	1.442	C37C20C9	111.585
C37C20	1.545	O45C30C15	110.32
O45C30	1.414	C46C32O16	109.676
C46C32	1.536	O47C32C46	111.842
O47C32	1.454	C66C46C32	113.506
C66C46	1.542	C69O47C32	110.994
C69O47	1.485	C84C66C46	106.946
C84C66	1.546	N59C37C20	115.303
N59C37	1.484	C65O45C30	115.244
C65O45	1.517	C78N59C37	112.973
C78N59	1.499	C80C65O45	104.917
C80C65	1.563	C97C78N59	114.951
C97C78	1.586	C4C2C1	111.352
C4C2	1.54	C10C3C1	113.636

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C10C3	1.535	O11C3C1	106.015
O11C3	1.477	C26C35O19	112.263
C26C35	1.535	C29C15C5	109.829
C29C15	1.541	C36C20C9	116.776
C36C20	1.542	O50C33C18	102.542
O50C33	1.481	C54C65O45	110.764
C54C65	1.527	C63C80C65	111.031
C63C80	1.538	N70C49C33	113.539
N70C49	1.487	C77N59C37	113.083
C77N59	1.478	O79C80C63	105.478
O79C80	1.473	C85C66C46	111.104
C85C66	1.537	O86C66C46	104.342
O86C66	1.471	C87C69O47	106.675
C87C69	1.523	C98C78N59	108.984
C98C78	1.543	O100C84C66	108.477
O100C84	1.465	O115C97C78	112.784
O115C97	1.471	H6C2C1	107.94
H6C2	1.093	H8C1C2	109.078
H8C1	1.084	H17C5C2	108.762
H17C5	1.098	H21C9C3	105.9
H21C9	1.094	H22C9C3	104.451
H22C9	1.097	H31C15C5	108.569
H31C15	1.093	H34C18O7	108.951
H34C18	1.087	H38C20C9	103.2
H38C20	1.1	O44C30C15	127.827
O44C30	1.225	H48C32O16	110.304
H48C32	1.096	H51C33C18	107.14
H51C33	1.092	H53C35O19	101.981
H53C35	1.095	H60C37C20	107.426
H60C37	1.095	H62C37C20	108.87
H62C37	1.098	H67C46C32	107.443
H67C46	1.091	H68C46C32	107.782
H68C46	1.096	H71C49C33	105.819
H71C49	1.114	H73C52C35	107.376
H73C52	1.094	H74C52C35	110.245
H74C52	1.092	H83C65O45	104.453
H83C65	1.093	H88C69O47	109.118
H88C69	1.091	H99C78N59	105.75
H99C78	1.094	H101C84C66	107.696
H101C84	1.1	H116C97C78	107.763
H116C97	1.097	C75C54C65	111.309
C75C54	1.543	H55C54C65	110.515
H55C54	1.088	H76C54C65	106.937
H76C54	1.096	C89N70C49	111.577
C89N70	1.487	C90N70C49	112.078
C90N70	1.488	C105O86C66	116.529
C105O86	1.472	H12C4C2	110.222

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H12C4	1.092	H13C4C2	109.877
H13C4	1.089	H14C4C2	108.409
H14C4	1.093	H23C10C3	109.559
H23C10	1.092	H24C10C3	112.16
H24C10	1.093	H25C10C3	108.752
H25C10	1.094	H27O11C3	102.474
H27O11	1.002	H28C26C35	110.578
H28C26	1.092	H39C26C35	108.986
H39C26	1.093	H40C26C35	109.481
H40C26	1.097	H41C29C15	110.579
H41C29	1.095	H42C29C15	109.527
H42C29	1.095	H43C29C15	109.399
H43C29	1.091	H56C36C20	111.343
H56C36	1.094	H57C36C20	108.72
H57C36	1.095	H58C36C20	111.252
H58C36	1.096	H61O79C80	103.194
H61O79	0.994	H64C63C80	110.71
H64C63	1.095	H81C63C80	107.469
H81C63	1.095	H82C63C80	109.397
H82C63	1.09	H72O50C33	106.862
H72O50	0.995	H91C75C54	110.585
H91C75	1.095	H92C75C54	109.736
H92C75	1.094	H93C75C54	111
H93C75	1.095	H94C77N59	109.016
H94C77	1.093	H95C77N59	114.045
H95C77	1.106	H96C77N59	109.695
H96C77	1.093	H102C85C66	109.928
H102C85	1.092	H103C85C66	109.873
H103C85	1.095	H104C85C66	109.641
H104C85	1.094	H106C87C69	110.007
H106C87	1.093	H107C87C69	110.096
H107C87	1.096	H108C87C69	109.549
H108C87	1.095	H109C89N70	110.519
H109C89	1.09	H110C89N70	108.174
H110C89	1.094	H111C89N70	112.571
H111C89	1.107	H112C90N70	112.895
H112C90	1.089	H113C90N70	107.938
H113C90	1.094	H114C90N70	111.985
H114C90	1.108	H117C98C78	107.92
H117C98	1.093	H118C98C78	112.232
H118C98	1.095	H119C98C78	110.845
H119C98	1.091	H120O100C84	108.004
H120O100	0.993	H121C105O86	111.775
H121C105	1.097	H122C105O86	110.992
H122C105	1.089	H123C105O86	104.602
H123C105	1.092	H124O115C97	108.03
H124O115	0.993		

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Table 5: Selected optimized bond lengths (Å) and bond angles (°) of chloroquine calculated using the B3LYP/6-311++G(d,p) basis set following full geometry optimization.

Chloroquine	Bond length Å	Chloroquine	Bond angles°
C18C13	1.432	C12C13C18	118.216
C12C13	1.453	C14C13C18	118.523
C14C13	1.419	C17C18C13	118.99
C17C18	1.421	N19C18C13	123.612
N19C18	1.372	C15C14C13	121.596
C15C14	1.379	C16C17C18	119.759
C16C17	1.365	C20N19C18	116.306
C20N19	1.33	C21C12C13	116.138
C21C12	1.397	N11C12C13	119.668
N11C12	1.369	Cl22C16C15	117.905
Cl22C16	1.833	H44C14C13	120.905
H44C14	1.084	H45C15C14	121.389
H45C15	1.081	H46C17C16	122.587
H46C17	1.08	H47C20N19	116.469
H47C20	1.086	H48C21C12	120.925
H48C21	1.077	C9N11C12	128.567
C9N11	1.486	H43N11C9	114.683
H43N11	1.012	C8C9N11	113.108
C8C9	1.551	C10C9C8	112.842
C10C9	1.546	H39C9C8	106.562
H39C9	1.097	C7C8C9	112.619
C7C8	1.541	H37C8C7	109.526
H37C8	1.095	H38C8C7	109.651
H38C8	1.098	C6C7C8	111.972
C6C7	1.543	H35C7C6	109.553
H35C7	1.098	H36C7C6	108.109
H36C7	1.094	N3C6C7	111.355
N3C6	1.481	H33C6N3	107.907
H33C6	1.095	H34C6N3	112.479
H34C6	1.105	C2N3C6	114.794
C2N3	1.484	C4N3C2	113.971
C4N3	1.483	C1C2N3	111.366
C1C2	1.541	H26C2C1	108.592
H26C2	1.096	H27C2C1	109.867
H27C2	1.104	C5C4N3	116
C5C4	1.551	H28C4N3	107.34
H28C4	1.097	H29C4N3	107.725
H29C4	1.096	H23C1C2	110.381
H23C1	1.096	H24C1C2	111.38
H24C1	1.095	H25C1C2	109.264
H25C1	1.093	H30C5C4	110.031
H30C5	1.096	H31C5C4	111.189
H31C5	1.095	H32C5C4	110.849
H32C5	1.095	H40C10C9	109.913
H40C10	1.094	H41C10C9	109.37
H41C10	1.095	H42C10C9	111.844
H42C10	1.092		

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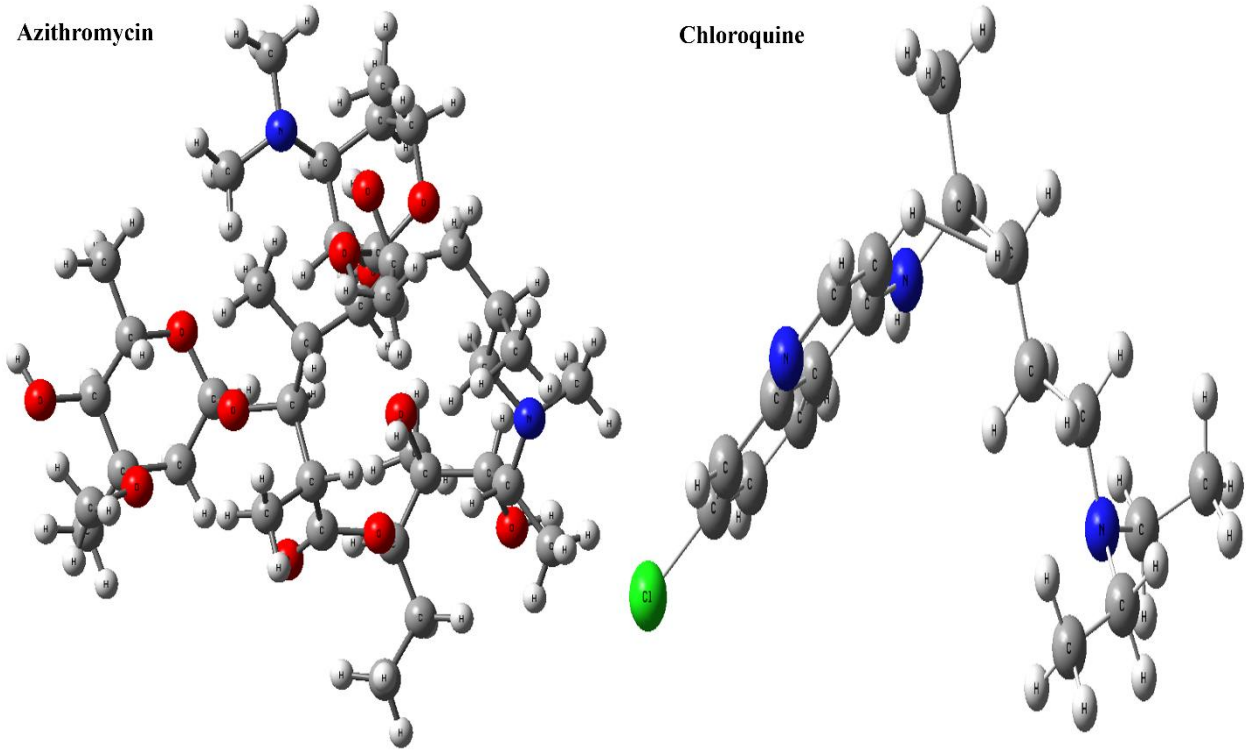

Figure 3. Optimized molecular geometries of the investigated compounds obtained using density functional theory (DFT) at the B3LYP/6-31G(d,p) level of theory. Geometry optimization was performed without symmetry constraints to obtain the minimum-energy conformations used for subsequent electronic structure, molecular orbital, and reactivity analyses.

Frontier Molecular Orbital (FMO) Analysis

Frontier molecular orbital analysis provides direct insight into the electronic excitation behavior and chemical reactivity of molecular systems. The calculated HOMO and LUMO energies (Table 3) indicate that azithromycin possesses a HOMO energy of −5.103 eV and a LUMO energy of −0.258 eV, resulting in a relatively large HOMO–LUMO energy gap (ΔE_{Gap}) of 4.845 eV. In contrast, chloroquine exhibits a deeper HOMO level (−5.216 eV) and a substantially lower LUMO level (−1.133 eV), yielding a smaller energy gap of 4.083 eV. The reduced energy gap in chloroquine implies a lower energetic barrier for intramolecular charge transfer, suggesting enhanced electronic polarizability and higher chemical reactivity. Conversely, the wider band gap of azithromycin reflects greater kinetic stability and reduced susceptibility toward electronic excitation [14,26].

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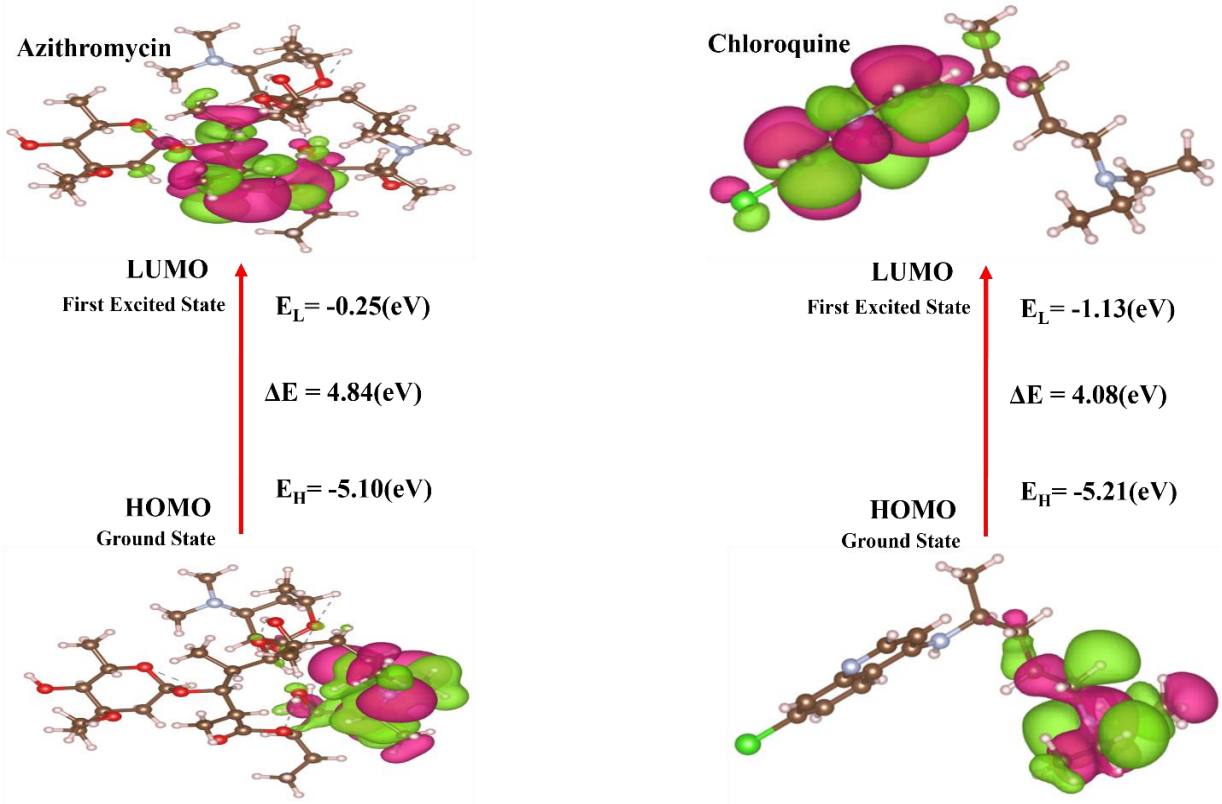

Figure 4. HOMO and LUMO orbital distributions of the DFT-optimized compounds calculated at the B3LYP/6-31G(d,p) level of theory. The frontier molecular orbitals illustrate the electronic distribution and energy gap governing molecular reactivity.

Quantum Chemical Reactivity Descriptors

The global reactivity descriptors derived from Koopmans' approximation further elucidate the intrinsic chemical behavior of both molecules. Chloroquine exhibits higher ionization potential (5.216 eV) and significantly greater electron affinity (1.133 eV) compared to azithromycin (5.103 eV and 0.258 eV, respectively), indicating a stronger tendency to accept electrons. This trend is reinforced by the higher electronegativity (χ = 3.175 eV) and more negative chemical potential (μ = −3.175 eV) of chloroquine, reflecting a greater thermodynamic driving force for electron uptake. Additionally, chloroquine shows lower global hardness (η = 2.042 eV) and higher softness (S = 0.49 eV^{-1}), characteristic of chemically softer systems with enhanced reactivity. The electrophilicity index (ω) further differentiates the two compounds, with chloroquine (2.47 eV) exhibiting a markedly stronger electrophilic character than azithromycin (1.48 eV), underscoring its superior ability to participate in charge-transfer-driven interactions [15,27].

Molecular Electrostatic Potential (MESP) Analysis

The molecular electrostatic potential distribution provides spatial insight into electrophilic and nucleophilic regions across the molecular surface. For azithromycin, the MESP is dominated by localized negative potential around oxygen atoms, particularly within hydroxyl and ether functionalities, while extensive aliphatic regions remain electrostatically neutral. This heterogeneous charge distribution contributes to localized interactions but limits global charge delocalization. In contrast, chloroquine displays more pronounced and delocalized negative potential over the nitrogen atoms of the quinoline ring and side-chain amine groups, accompanied by electron-deficient regions near the aromatic framework. This complementary distribution facilitates stronger electrostatic interactions with surrounding chemical or biological environments, consistent with its higher electrophilicity and softness derived from quantum descriptors [16,17].

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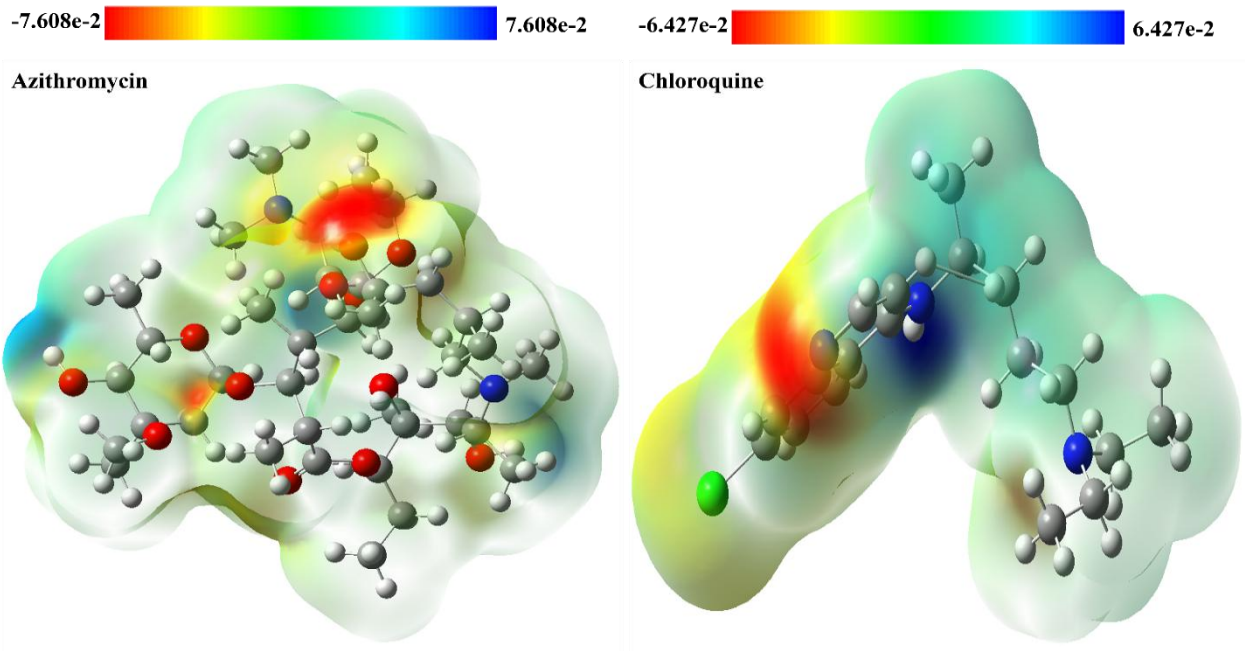

Figure 5. Molecular electrostatic potential (MESP) surfaces of the optimized compounds obtained from DFT calculations. The color-coded maps identify regions of negative and positive electrostatic potential, highlighting the preferred sites for electrophilic and nucleophilic interactions.

Correlation Between DFT Descriptors and Clinical Efficacy

The comparatively lower reactivity of azithromycin arises from a combination of electronic and structural factors. Its significantly larger HOMO–LUMO gap indicates reduced ease of electronic excitation and charge transfer. The higher global hardness and lower softness further reflect resistance to deformation of the electron cloud during chemical interactions. Moreover, the lower electron affinity and electrophilicity index suggest a weaker tendency to accept electrons, limiting its participation in electrophilic processes [18,19,20]. Structurally, the flexible macrocyclic framework of azithromycin promotes conformational stability but disperses electronic density over a large molecular volume, reducing effective charge concentration. In contrast, chloroquine's smaller energy gap, higher softness, and greater electrophilicity—combined with a more rigid, conjugated framework—collectively enhance its chemical reactivity. These results consistently explain why azithromycin is electronically more stable and less reactive than chloroquine, in full agreement with the computed DFT descriptors [21].

Table 6: Global quantum chemical reactivity descriptors of azithromycin and chloroquine, including ionization potential (IP), electron affinity (EA), electronegativity (χ), chemical potential (μ), global hardness (η), softness (S), and electrophilicity index (ω), derived from DFT calculations.

Descriptor	Azithromycin	Chloroquine
HOMO (eV)	−5.103	−5.216
LUMO (eV)	−0.258	−1.133
ΔE_{Gap} (eV)	4.845	4.083
Ionization Potential, IP	5.103	5.216
Electron Affinity, EA	0.258	1.133
Electronegativity, χ	2.681	3.175
Chemical Potential, μ	−2.681	−3.175
Hardness, η	2.423	2.042
Softness, S	0.413	0.49
Electrophilicity, ω	1.48	2.47

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Discussion

In the present randomized controlled study, oral chloroquine demonstrated a markedly higher overall efficacy (90%) compared with oral azithromycin (60%) in the treatment of cutaneous leishmaniasis. This statistically significant difference ($p = 0.015$) indicates superior therapeutic performance of chloroquine under the dosing regimen employed. Clinically, chloroquine has long been recognized for its antiparasitic activity, primarily mediated through accumulation within acidic parasitophorous vacuoles, where it interferes with intracellular metabolic pathways essential for parasite survival. In contrast, azithromycin, while effective against several intracellular pathogens, exhibits comparatively limited direct leishmanicidal activity, which may partially explain its lower cure rate observed in this study.

Stratified analysis further highlighted that chloroquine maintained consistently high efficacy across age groups, with cure rates of 90% in both younger (18–40 years) and older (41–60 years) patients. Although differences between treatment arms did not reach statistical significance in these subgroups, the consistently higher response to chloroquine suggests robustness across demographic categories. Similarly, chloroquine showed superior efficacy in both male and female patients, with a particularly pronounced difference in females, where azithromycin demonstrated substantially reduced effectiveness. These findings suggest that chloroquine's therapeutic action may be less influenced by host-related biological variability compared to azithromycin.

Disease duration emerged as an important determinant of treatment response. Patients with lesions of 1–3 months' duration achieved a 100% cure rate with chloroquine, significantly exceeding the response observed with azithromycin (68.8%; $p = 0.018$). This supports the concept that early intervention enhances therapeutic success, likely due to lower parasite burden and reduced tissue remodeling in early-stage disease. Comparable observations have been reported in earlier studies, where shorter disease duration was associated with improved outcomes following antileishmanial therapy.

Lesion site also significantly influenced treatment efficacy. Chloroquine achieved complete healing in all patients with lesions on the hands and arms, significantly outperforming azithromycin ($p = 0.009$). A similar, though not statistically significant, trend was observed for lesions on the feet and legs. In contrast, neither drug demonstrated efficacy against body lesions. The superior response observed in extremity lesions may reflect better vascularization, improved drug delivery, and a more favorable local immune microenvironment. Conversely, the poor response of body lesions may be attributable to reduced drug penetration, deeper tissue involvement, or altered host–parasite interactions at these sites.

The present findings are broadly consistent with earlier clinical reports demonstrating high efficacy of oral chloroquine in cutaneous leishmaniasis, although reported cure rates vary across studies. Differences in Leishmania species, geographic distribution, host immunity, and treatment protocols likely contribute to these discrepancies. Similarly, the moderate efficacy of azithromycin observed here contrasts with higher cure rates reported in some previous studies, underscoring the influence of parasite species and local epidemiological factors. The absence of species identification in the present study represents a limitation and may partly explain variability in treatment response.

Despite its strengths, this study has several limitations. Its single-center design and relatively small sample size may limit generalizability. The exclusion of standard antimonial therapy as a comparator restricts broader therapeutic comparison. Additionally, the absence of long-term follow-up precludes assessment of relapse rates and sustained cure. Future multicenter studies incorporating parasite species identification, larger cohorts, and extended follow-up are warranted to validate and extend these findings.

Integration of DFT findings with clinical outcomes

Importantly, the observed clinical superiority of chloroquine is strongly supported by density functional theory (DFT) analysis performed in this study. Chloroquine exhibited a smaller HOMO–LUMO energy gap, lower global hardness, higher

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softness, and a significantly greater electrophilicity index compared with azithromycin. These quantum chemical descriptors indicate enhanced electronic reactivity and greater charge-transfer capability, properties that are critical for effective interaction with biological targets and intracellular parasite compartments. In contrast, azithromycin showed a larger energy gap, higher hardness, and lower electrophilicity, reflecting greater electronic stability but reduced chemical reactivity. Molecular electrostatic potential analysis further revealed more favorable charge delocalization in chloroquine, supporting stronger intermolecular interactions. Together, these DFT-derived characteristics provide a mechanistic explanation for the higher clinical efficacy of chloroquine and the comparatively limited performance of azithromycin. The integration of computational and clinical findings in this study underscores the value of a clinico–computational approach for rationalizing drug efficacy and guiding therapeutic decision-making in cutaneous leishmaniasis.

Conclusion

This study demonstrates that oral chloroquine is a highly effective therapeutic option for cutaneous leishmaniasis, significantly outperforming oral azithromycin under the treatment conditions evaluated. Clinically, chloroquine exhibited consistent efficacy across age and gender groups and achieved particularly favorable outcomes in patients with early-stage disease and lesions located on the extremities. In contrast, azithromycin showed only moderate overall efficacy and markedly reduced effectiveness in specific subgroups, including female patients and those with body lesions.The observed clinical superiority of chloroquine is further substantiated by density functional theory (DFT) analysis. Chloroquine displayed enhanced electronic reactivity, characterized by a smaller HOMO–LUMO energy gap, greater softness, and higher electrophilicity compared with azithromycin. These molecular features indicate a stronger capacity for charge transfer and intermolecular interactions, providing a mechanistic basis for its improved antileishmanial performance. Conversely, the larger energy gap and higher electronic stability of azithromycin, while contributing to its favorable safety profile, likely limit its chemical reactivity and therapeutic effectiveness.By integrating randomized clinical outcomes with quantum chemical descriptors, this work establishes a clear molecular rationale for differential treatment responses in cutaneous leishmaniasis. These findings support the preferential use of oral chloroquine as an accessible and effective therapeutic alternative in endemic and resource-limited settings, while highlighting the value of clinico–computational approaches in guiding evidence-based treatment strategies and future drug optimization.

Ethical Approval

The study protocol was approved by the Ethical Review Board of the PIMS HOSPITAL ISLAMABAD (Reference Number: F-5-2/2024(ERRC)/PIMS)

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Author contributions statement:

Urfa Nisar: Conceptualization, study design, methodology, clinical investigation, data collection, synthesis and characterization of the investigated compounds, data curation, and original draft preparation. **Hira Virk, Nishwa Khan, Muhammad Tarif Saif, Muhammad Saqib and Dr. Naureena Munawer:** Project supervision, conceptualization, formal analysis, data interpretation, validation, manuscript review and editing, funding acquisition, and final approval of the manuscript. **Jamaluddin Mahar, Muhammad Zahid khan:**In vitro experimental studies, data acquisition, and interpretation of the experimental findings. **Muhammad Amir Abbas:** Density functional theory (DFT) and in silico analyses, validation and interpretation of computational and spectral characterization data, visualization, preparation of the initial computational draft, and manuscript review and editing.

Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of conflict of interest

The authors declare no conflict of interest, financial or otherwise. No writing assistance was utilized in the production of this manuscript.

Consent for publication

All authors have read and approved the final version of the manuscript.

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