Chemical Science International Journal

29(5): 51-60, 2020; Article no.CSIJ.58964
ISSN: 2456-706X
(Past name: American Chemical Science Journal, Past ISSN: 2249-0205)

Comparative Theoretical Study of Stability, Lypophilicity, Dipole Moments, Acidity and Spectroscopic Properties of Non-Steroidal Anti-Inflammatory Drugs: Ibuprofen, Ketoprofen and Flurbiprofen

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Authors' contributions

This work was carried out in collaboration among all authors. All the authors contributed to the realization of this work and have knowledge of final version. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/CSJI/2020/v29i530180
Editor(s):
(1) Pradip K. Bhowmik, University of Nevada, Nevada.
(2) Dr. Thomas P. West, Texas A&M University, USA.
Reviewers:
(1) Beena Kumari, Indira Gandhi University, India.
(2) Dhananjay Babanrao Deshmukh, Dr. Babasaheb Ambedkar Technological University, India.
(3) Sankar Annamalai, MAHER - Meenakshi Academy of Higher Education and Research, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/58964

Original Research Article

Received 10 May 2020
Accepted 16 July 2020
Published 30 July 2020

ABSTRACT

A comparative theoretical study of some physicochemical properties of R and S enantiomers of ibuprofen, ketoprofen and flurbiprofen is undertaken in order to understand their reactivity. To do this, DFT and TD-DFT methods at the B3LYP/6-311G(d,p) level theory are used. The partition coefficient determined is 3.72 for ibuprofen, 2.81 for ketoprofen and 4.12. for flurbiprofen. That means that these NSAIDs are characterized by a high lipophilicity. The calculated Gibbs energies show that the R enantiomer is the most stable in the case of ibuprofen and the S enantiomer in the case of ketoprofen and flurbiprofen. The study of acidity shows that S enantiomer of ibuprofen and

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R enantiomers of ketoprofen and flurbiprofen are the most acidic enantiomers. TD-DFT calculations show that, the absorption maxima (λmax) of ibuprofen and flurbiprofen correspond to the HOMO→LUMO transition. For ketoprofen, these are associated with the transition HOMO→LUMO+1. These results elucidate the reactivity of the investigated NSAIDs and could help to establish a classification their efficacy.

Keywords: Ibuprofen; ketoprofen; flurbiprofen; acidity; B3LYP.

1. INTRODUCTION

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are one of the most widely used therapeutic classes in the world due to their antipyretic, analgesic and anti-inflammatory activity. Their pharmacological activity relies on the inhibition of the COX-1 and COX-2 activity [1-3]. It is estimated that more than 30 million people use NSAIDs daily. However, the use of NSAIDs exposes patients to numerous adverse effects via cutaneous, digestive, hepatic, renal, cardiovascular toxicity [4-9]. This study focuses on the NSAIDs ibuprofen, ketoprofen and flurbiprofen as they are among the most commonly used NSAIDs [10-12]. They are applied topically in the treatment of traumatic, overstress, or inflammatory changes in periarticular tissues and muscles as well as for the treatment of inflammations in the oropharyngeal cavity or the dental pain. Due to the analgesic activity, the investigated drugs are used in the treatment of muscular pains, after tooth extraction, after surgery, inneuralgia….in neuralgina, in root syndromes, in discopathy, and also in migraine [13-15]. In 2013, ibuprofen was the second best-selling molecule in France. However, pharmacoepidemiological and experimental studies have revealed serious bacterial complications with ibuprofen and ketoprofen used for fever or non-rheumatic pain [16]. In the fight against the corona virus pandemic (covid-19), it has been revealed that taking NSAIDs [17,18], especially ibuprofen could be a factor aggravating the infection [19-21].

This study therefore provides theoretical data on the physicochemical properties of the R and S enantiomers of the NSAIDs ibuprofen, ketoprofen and flurbiprofen for which there is a relatively small amount of experimental physicochemical data. The results could shed light on their mechanism of action and thus minimize their serious undesirable effects. For this purpose, parameters such as lipophilicity, dipole moment, acidity, spectroscopic properties were determined.

2. MATERIALS AND METHODS

2.1 Level of Calculation Theory

The calculations are carried out with the GAUSSIAN-09 program [22] and the freeware ChemSketch of Advanced Chemistry Development, Inc : ACD/ChemSketch. The ground state geometries of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have been studied using the Becke's three parameter exact exchange functional (B3) [23] combined with gradient corrected correlation functional of Lee-Yang-Parr (LYP) [24] of density functional theory, using 6-311G(d,p) basis set. The aqueous phase calculations are carried out using Tomasi's polarizable continuum model (PCM) [25]. The Gibbs free energies are obtained from the calculation of the frequencies. Frequency analyses were proceeded to confirm the structure being a minimum or a transition state (i.e. without or with solely an imaginary frequency). The freeware ACD/ChemSketch is used for LogP calculation. The absorption spectrum are calculated using TD-DFT….Time-Dependent Density Functional Theory (TD-DFT) method at B3LYP/6-311G(d,p) level of theory [26,27].

2.2 Stability

The relative stability of the R and S enantiomers of NSAIDs is determined from the Gibbs free energy. It is calculated from the following equation:

$$G(298K) = E_e + G_{corr} \quad (1)$$

E_e is the total electronic energy of the molecule.
G_{corr} is the thermal correction to Gibbs free energy of the molecule.

The enantiomer which has the lowest Gibbs free energy is the most stable.

2.3 Lipophilicity and Dipole Moments

Lipophilicity is defined as the affinity of a molecule or moiety to a lipophilic environment

[28]. Lipophilicity affects the biological activity of a drug because it plays a significant role in drug interactions with the receptor, the pharmacokinetics of the molecule, its toxic action, and in the pharmaceutical aspect, the solubility of the substance [29]. It has often been used as a criterion for comparing several drugs [30-32]. It is an important parameter described by the partition coefficient which is usually denoted as the logarithm of P (LogP). The freeware ACD/ChemSketch was used to calculate LogP. Higher the LogP, the compound will be more lipophilic.

The electric dipole moment characterizes the distribution of charges in a molecule. The knowledge of this distribution is fundamental to understanding the electronic properties of the molecule, its geometry, interactions with other particles. In a static electric field, total dipole moment is given by the following Taylor series:

$$\mu_{tot} \rightarrow \mu_0 + \alpha E + \cdots \quad (2)$$

μ_0 is the permanent dipole moment
α is the electronic polarizability tensor
αE is the induced dipole moment

2.4 Acidity

For acidity, varying Gibbs free energy of the deprotonation reaction helps to evaluate the acidity of NSAIDs [33]. It may be calculated from the following equations:

$$AH \rightarrow A^- + H^+ \quad (3)$$

$$\Delta G = G(A^-) + G(H^+) - G(AH) \quad (4)$$

In gas phase, $Gg(H^+)$ = 2.5RT − TΔS = 1.48 − 7.76 = −6.28 kcal/mol [34,35].

That method has been used to determine the acidity of several molecules [36-39].

2.5 Spectroscopic Properties

Frontier molecular orbitals (FMOs) known as highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) respectively, plays a vital role in chemical reactions of any molecule, as well as absorption spectra [40,41]. Indeed the HOMO and LUMO energy gap explains the chemical hardness, chemical potential, reactivity, kinetic stability, optical polarizability, chemical softness, electronegativity, electrophilicity etc. of a molecule. Here we are focussed to calculate the chemical hardness (η) of NSAIDs by using HOMO and LUMO energies. According to Koopman's theorem [42] associated within the framework of HF self-consistent field molecular orbital theory, the ionization energy (I) and electron affinity (A) can be stated through HOMO and LUMO orbital energies as:

$$I = -E_{HOMO} \quad (5)$$

$$A = -E_{LUMO} \quad (6)$$

The chemical Hardness (η) of a molecule is calculated by:

$$\Delta E = E_{LUMO} - E_{HOMO} \quad (7)$$

$$\eta = \frac{1}{2}(\Delta E) \quad (8)$$

Then the spectral studies of NSAIDs have been performed using TD-DFT at B3LYP/6-311G(d,p) level of theory in gas phase. TD-DFT is a reliable method for the excited state computation that provides accurate results [43-45]. To obtain the nature and energy of the singlet-singlet electronic transition, the prediction of the first 3 excited states are performed. Absorption energy, corresponding oscillator strength and orbital coefficients were calculated.

3. RESULTS AND DISCUSSION

The results concern the stability, the lipophilicity, the dipole moments, the acidity, and the spectroscopic properties of R and S enantiomers of ibuprofen, ketoprofen and flurbiprofen. These results will make it possible to compare their reactivity.

3.1 Stability

The Gibbs free energy at computational level B3LYP/6-311G(d, p), helps to discuss the relative stability of R and S enantiomers of ibuprofen, kétoprofen and flurbiprofen shown in Fig. 1.

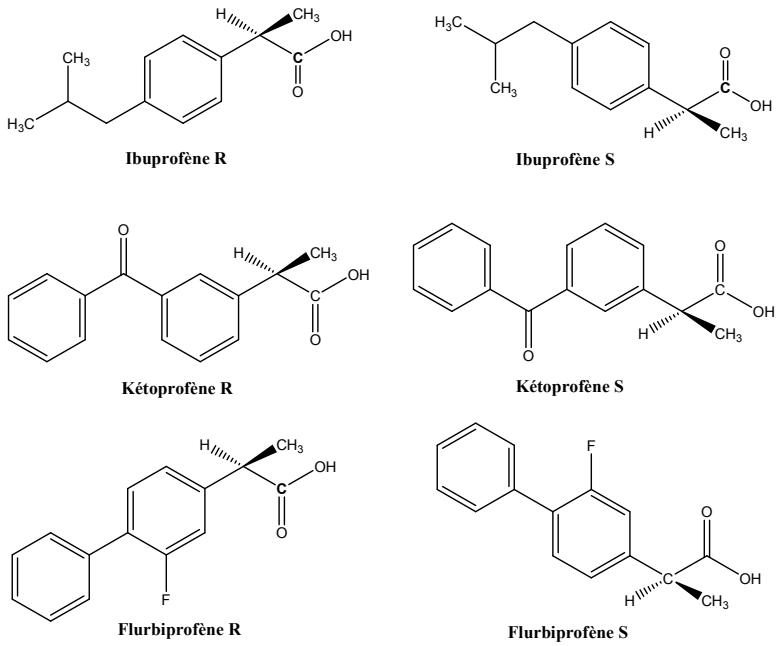

Fig. 1. R and S enantiomers of ibuprofen, ketoprofen and flurbiprofen

Table 1 summarizes the Gibbs free energy values and the Gibbs free energy difference between the two enantiomers of each NSAID (ΔG). The discussion focuses on the gas phase at first. Results in Table 1 show that R-ibuprofen is 3.73 Kcal/mol more stable than S-ibuprofen. S-Ketoprofen is 1.16 Kcal/mol more stable than its R enantiomer. As for flurbiprofen, the S enantiomer is 4.19 Kcal/mol more stable that the R enantiomer. In the aqueous phase, the same order of stability is observed but with different energy differences. Indeed, ketoprofen and flurbiprofen stabilize very clearly in the aqueous phase compared to ibuprofen. This could be explained by the establishment of hydrogen bonds between oxygen atom of ketoprofen and fluorine atom of flurbiprofen with water molecules. Furthermore, the more stable a molecule, the less it reacts. Thus S-ibuprofen would be more reactive than R-ibuprofen; R-ketoprofen would be more reactive than S-ketoprofen. Similarly, R-flurbiprofen would be more reactive than S-flurbiprofen. Our results are in agreement with previous studies [46,47].

3.2 Lipophilicity and Dipole Moments

Calculated lipophilicity (LogP) parameters and dipole moments are shown in Table 2. The LogP value calculated of ibuprofen is 3.72, that of ketoprofen is 2.81 and that of flurbiprofen is 4.12. The experimentally measured LogP has been reported as 3.97 for ibuprofen, 3.12 for ketoprofen and 4.16 for Flurbiprofen [48]. The values calculated from the freeware ACD/ChemSketch, are therefore in agreement with the experimental values. These NSAIDs are characterized by a high lipophilicity allowing them to pass easily through biological membranes. That high lipophilicity also explains their strong affinity for many tissues. However the most lipophilic compounds are flurbiprofen and ibuprofen. The lower LogP value of ketoprofen results from the presence of an additional oxygen atom, which is an acceptor of hydrogen bonds. This observation is in agreement with that of other theoretical studies [28].

Values of the dipole moment in the gas phase show that S-ibuprofen, with a dipole moment of 5.07 D, is more polar than R-ibuprofen (1.62 D). R-Ketoprofen with a dipole moment of 4.41 D is more polar than S-Ketoprofen (4.09 D) and R-flurbiprofen, with a dipole moment of 3.86 D, is more polar than S-flurbiprofen (2.47 D). The same observations are made in the aqueous phase but with a clear increase in values. Furthermore, in the gas phase, ibuprofen has the highest dipole moment, while in the aqueous phase the highest dipole moment is observed with ketoprofen. The higher dipole moment of ketoprofen results from the presence of an additional oxygen atom, which is an acceptor of hydrogen bonds. The earlier studies also show that the dipole moment would be enhanced during the formation of hydrogen bonds [49].

Table 1. Gibbs free energy G and ΔG

Compounds	B3LYP-gas		B3LYP-PCM	
	G (Kca/mol)	ΔG(Kca/mol)	G (Kca/mol)	ΔG(Kca/mol)
R-ibuprofen	-412051.248	0.000	-412063.982	0.00
S-ibuprofen	-412047.515	3,733	-412053.452	10.530
R-ketoprofen	-529513.028	1,165	-529521.832	0.833
S-ketoprofen	-529514.193	0.000	-529522,665	0.000
R-flurbiprofen	-520676.751	4.189	-520685.063	2.607
S-flurbiprofen	-520680.940	0.000	-520687.670	0.000

Table 2. Calculated and experimental lipophilicity (LogP) parameters and dipole moments (μ)

Compounds	Log P	Log P_{Exp}[48]	μ_{gas}(D)	$\mu_{aq\text{-}PCM}$(D)
R-ibuprofen	3.72±0.23	3,97	1.62	2.48
S-ibuprofen	3.72±0.23		5.07	5.67
R-ketoprofen	2.81±0.33	3.12	4.41	6.14
S-ketoprofen	2.81±0.33		4.09	5.96
R-flurbiprofen	4.12±0.37	4.16	3.86	4.10
S-flurbiprofen	4.12±0.37		2.47	3.44

3.3 Acidity

It is known that most of the anti-inflammatory drugs are carboxylic acids in which the carboxylic group is available for metal-ligand interactions [50,51]. Indeed, the carboxylic acid group is ionizable at physiological pH. The anionic charge allows the NSAID to be fixed in the catalytic site by establishing an electrostatic interaction with a positively charged cox-enzyme residue. It is important to know their acidic characteristics. Table 3 presents the results of the calculations. Weaker the ΔG, the oxygen atom will be more acidic. Under these conditions, in the gas phase, S-ibuprofen is more acidic than R-ibuprofen, R-ketoprofen is more acidic than S-ketoprofen and R-flurbiprofen is more acidic than S-flurbiprofen. These results corroborate those of stability and dipole moments.

3.4 Spectroscopic Properties

In this part, we analyzed the frontier molecular orbitals and absorption properties.

3.4.1 Frontier Molecular Orbitals (FMOs)

The calculated values of HOMO and LUMO energy (E), their energy gap (ΔE) and chemical Hardness (η) are presented in Table 4. Higher HOMO energy corresponds to the more reactive molecule in the reactions with electrophiles, while lower LUMO energy is essential for molecular reactions with nucleophiles [52]. According to softness-hardness rule, a large HOMO-LUMO energy gap correspond to hard molecules and a small HOMO-LUMO energy gap is associated to soft molecules [53,54]. In other words, a small energy gap leads to high polarizability, and a large gap means low polarizability. The HOMO-LUMO energy gap of R-ibuprofen is found to be 4.717 eV with chemical hardness value 2.358 eV. The HOMO-LUMO energy gap of S-ibuprofen is 4.683 eV with chemical hardness value 2.342 eV. S-Ibuprofen is therefore more polarizable than R-ibuprofen. Likewise R-ketoprofen with energy gap of 1.904 eV is therefore more polarizable than S-ketoprofen (1.920 eV). R-flurbiprofen with energy gap of 1.841 eV is therefore more polarizable than S-flurbiprofen (1.847eV). S-ibuprofen, R-ketoprofen and R-flurbiprofen therefore have high chemical reactivity compared to their corresponding enantiomers.

3.4.2 Absorption properties

TD-DFT method at B3LYP/6-311G(d,p) level of theory is used to perform the spectral study of ibuprofen, ketoprofen and flurbiprofen in gas phase. The calculated absorption energy, corresponding oscillator strength and orbital coefficients are summarized in Table 5. The results show that for all the compounds, the lowest energy transition is due to the excitation of electron from HOMO to the LUMO (H→L) except that of R-ibuprofen which corresponds to the transition H→ L+1. Fig. 2 shows the variation of the absorption energies as a function of the oscillator strength. The absorption intensity is directly related with the dimensionless oscillator strength and the dominant absorption bands are the transitions with higher oscillator strength

value [55]. The absorption spectra of the three NSAIDs have only one peak. The absorption maxima (λmax) of ibuprofen and flurbiprofen correspond to the H→L transition. That of ketoprofen is associated to the H→L+1 transition. The peak of R-ibuprofen is observed at 5.492 eV (226 nm), this.that of S-ibuprofen is observed at 5.653 eV (219 nm). The peak of R-ketoprofen is observed at 4.457 eV (278 nm), this of S-ketoprofen is observed at 4.479 eV (277 nm). The peak of R-flurbiprofen is observed at 4.734 eV (262 nm), this of S-flurbiprofen is observed at 4.741 eV (261 nm). The absorption maxima (λmax) of R enantiomer are found to exhibit a red shift compared with the λmax of S enantiomer of 7 nm, for ibuprofen and 1 nm for ketoprofen and flurbiprofen. In addition, the absorption energies of the R and S enantiomers of ketoprofen are lower than those of the R and S enantiomers of flurbiprofen followed by those of the R and S enantiomers of ibuprofen.

Table 3. Gas phase acidity

Compounds	G (Kj/mol)	ΔG (Kj/mol)
R-ibuprofene	-1722374.217	1714.283
R-ibuprofene (O-anion)	-1720633.684	
S-ibuprofene	-1722358.613	1695.539
S-ibuprofene (O-anion)	-1720636.823	
R-ketoprofene	-2213364.459	1711.532
R-ketoprofene (O-anion)	-2211626.677	
S-ketoprofene	-2213369.327	1715.949
S-ketoprofene (O-anion)	-2211627.128	
R-flurbiprofene	-2176428.818	1696.429
R-flurbiprofene (O-anion)	-2174706.139	
S-flurbiprofene	-2176446.329	1716.277
S-flurbiprofene (O-anion)	-2174703.802	

Table 4. Molecular orbital energies (E), energy gap ΔE and hardness η in gas phase

Compounds	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	η (eV)
R-ibuprofen	-9.814	-5.098	4.717	2.358
S-ibuprofen	-9.805	-5.122	4.683	2.342
R-ketoprofen	-9.958	-6.151	3.808	1.904
S-ketoprofen	-9.980	-6.139	3.841	1.920
R-flurbiprofen	-9.256	-5.575	3.682	1.841
S-flurbiprofen	-9.277	-5.583	3.694	1.847

Table 5. Absorption energy and oscillator strengths in gas phase

Compounds	Orbital transitions	Absorption energy		Oscillator strength
		ʎ (nm)	eV	f (a,u)
R-ibuprofen	H→L+1 (0.544)	239	5.193	0.003
	H→L (0.575)	226	5.492	0.161
	H-2→L (0.443)	212	5.851	0.033
S-ibuprofen	H→L (0.441)	240	5.160	0.004
	H→L+2 (0.418)	223	5.568	0.071
	H→L (0.399)	219	5.653	0.112
R-ketoprofen	H→L (0.627)	344	3.603	0.001
	H-1→L (0.653)	278	4.457	0.018
	H-3→L (0.555)	269	4.610	0.010
S-ketoprofen	H→L (0.631)	344	3.603	0.001
	H-1→L (0.651)	277	4.479	0.016
	H-2→L (0.523)	268	4.623	0.012
R-flurbiprofen	H→L (0.632)	262	4.734	0.420
	H→L+1 (0.488)	250	4.954	0.154
	H-1→L (0.574)	250	4.958	0.009
S-flurbiprofen	H→L (0.639)	261	4.741	0.430
	H-2→L (0.458)	250	4.966	0.139
	H-1→L (0.532)	249	4.986	0.012

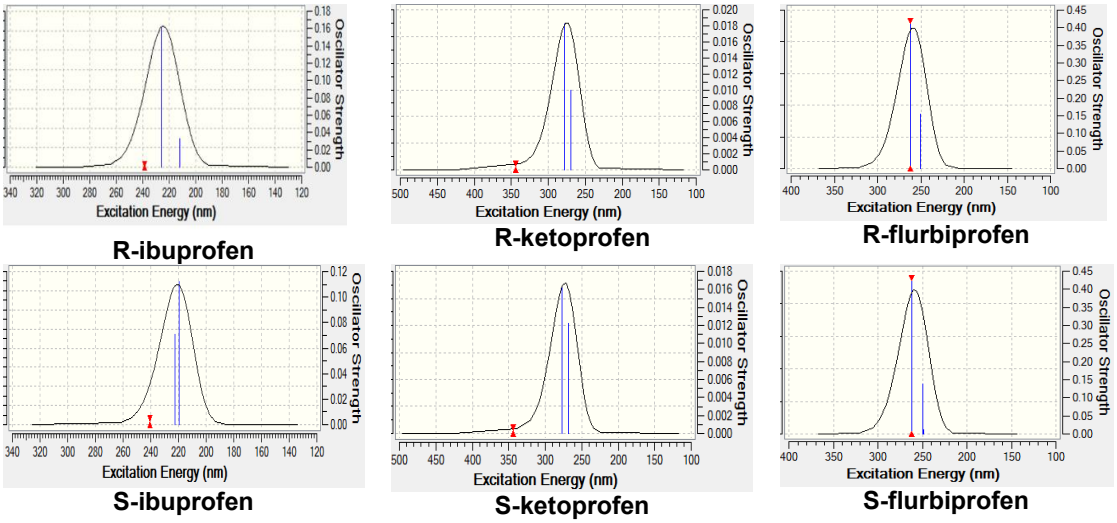

Fig. 2. Absorption spectra of R, S enantiomers of ibuprofen, ketoprofen and flurbiprofen

4. CONCLUSION

This theoretical study set out to determine the stability, lipophilicity, dipole moment, acidity and spectroscopic properties of R and S enantiomers of ibuprofen, ketoprofen and flurbiprofen. Using DFT and TD-DFT methods, the following conclusions can be drawn.

The study of the stability reveals that R-ibuprofen is more stable than S-ibuprofen; R-Ketoprofen is more stable than S-ketoprofen and R-flurbiprofen is more stable than S-flurbiprofen.

The lipophilicity study shows that ibuprofen, ketoprofen and flurbiprofen are very lipophilic. However the most lipophilic is flurbiprofen and the least lipophilic is ketoprofen.

The evaluation of the polarity through the dipole moment shows that S-ibuprofen is more polar than R-ibuprofen, R-Ketoprofen is more polar than S-ketoprofen and R-flurbiprofen, is more polar than S-flurbiprofen.

In terms of acidity, research establishes that in the gas phase, S-ibuprofen is more acidic than R-ibuprofen; R-Ketoprofen is more acidic than S-ketoprofen and R-flurbiprofen, is more acidic than S-flurbiprofen.

The energy gap indicates that S-ibuprofen is more reactive than R-ibuprofen; R-ketoprofen is more reactive than S-ketoprofen and R-flurbiprofen is more reactive than S-flurbiprofen. This result is in perfect agreement with those of dipole moment and acidity.

TD-DFT results show that for all the compounds, absorption spectra have only one peak. The absorption maxima (λmax) of ibuprofen and flurbiprofen correspond to the HOMO→LUMO transition. These of ketoprofen are associated to the HOMO→LUMO+1 transition.
Moreover, this work opens new perspectives; in particular its results could help to establish a classification of efficacy of NSAIDs.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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